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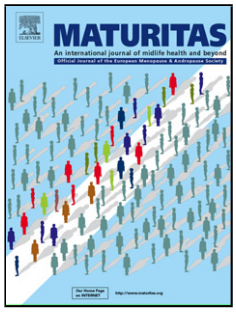

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Interventions to reduce the risk of ovarian and fallopian tube cancer: A European Menopause and Andropause Society Position Statement

1. Faustino R. Pérez-López, Department of Obstetrics and Gynecology, Zaragoza University Faculty of Medicine, Lozano-Blesa University Hospital, Zaragoza 50009, Spain
2. Iuliana Ceausu, Department of Obstetrics and Gynecology, 'Carol Davila' University of Medicine and Pharmacy, and Department of Obstetrics and Gynecology, 'Dr. I. Cantacuzino' Hospital, Bucharest, Romania
3. Herman Depypere, Breast Clinic and Menopause Clinic, University Hospital, De Pintelaan 185, 9000 Gent, Belgium
4. Sean Kehoe, Lawson Tait Professor of Gynaecological Cancer, Institute of Cancer and Genomics, University of Birmingham UK
5. Irene Lambrinoudaki, Second Department of Obstetrics and Gynecology, National and Kapodestrian University of Athens, Greece
6. Alfred Mueck, University Women's Hospital of Tuebingen, Calwer Street 7, 72076 Tuebingen, Germany
7. Levent M. Senturk, Istanbul University Cerrahpasa School of Medicine. Dept. of Obstetrics and Gynecology, Division of Reproductive Endocrinology, IVF Unit, Istanbul, Turkey
8. Tommaso Simoncini, Department of Clinical and Experimental Medicine, University of Pisa, Via Roma, 67, 56100, Pisa, Italy
9. John C. Stevenson, National Heart and Lung Institute, Imperial College London, Royal Brompton Hospital, London SW3 6NP, UK
10. Petra Stute, Department of Obstetrics and Gynecology, University Women's Hospital, Bern, Switzerland
11. Margaret Rees, Women's Centre, John Radcliffe Hospital, Oxford OX3 9DU, UK

Corresponding author

Faustino R. Pérez-López, Department of Obstetrics and Gynecology, Zaragoza University Faculty of Medicine, Lozano-Blesa University Hospital, Zaragoza 50009, Spain

faustino.perez@unizar.es

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Highlights

- Approximately 1.3% of women will be diagnosed with ovarian cancer at some point during their lifetime. It has a high mortality, with a 5-year survival rate of 46%.
- Preventive oophorectomy is associated with an 80% reduction in the risk of ovarian, fallopian tube, or peritoneal cancer in BRCA1 or BRCA2 gene mutation carriers and with a 77% reduction in all-cause mortality.
- Evidence indicates that opportunistic bilateral salpingectomy may prevent ovarian cancer. Bilateral salpingectomy should be preferred to tubal ligation, and should be recommended in cases of hysterectomy for benign conditions.
- Combined but not progestogen-only contraceptive medication reduces the risk of ovarian cancer.
- Women should be advised that being overweight or obese increases the risk of ovarian cancer. There is no evidence that any particular diet reduces the risk of ovarian cancer.
- Menopausal hormone therapy should be individualized in oophorectomized BRCA gene mutation carriers or among those with other genetic-related increased ovarian cancer risk.

Abstract:

Background: Ovarian cancer is a leading cause of female gynecological cancer-related death, and there are no effective screening procedures or early diagnostic approaches.

Aims: To examine risk factors and risk-reducing strategies for both sporadic and familial tumors.

Materials and methods: Literature review and consensus of expert opinion.

Results and conclusions: In women with a genetic predisposition to ovarian cancer, salpingo-oophorectomy reduces the risk of ovarian malignancy, and to a lesser degree of breast cancer. Opportunistic bilateral salpingo-oophorectomy and bilateral salpingectomy may also prevent epithelial ovarian cancer. In premenopausal women, bilateral salpingectomy should be preferred to tubal ligation, and be performed when hysterectomy is carried out for benign uterine disease. Hysterectomy and the use of combined oral contraceptives and non-steroid

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anti-inflammatory drugs are also recognized to reduce the risk of ovarian cancer, as do the prevention of obesity and smoking cessation.

Key words: Ovarian cancer, fallopian tubes cancer, ovarian borderline tumors, BRCA gene mutation, bilateral salpingectomy, bilateral oophorectomy, combined oral contraceptives, hysterectomy, non-steroid anti-inflammatory drugs, obesity, smoking

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1. Background

Approximately 1.3% of women will be diagnosed with ovarian cancer at some point during their life. Mortality is high, with a 5-year survival rate ranging from 36% to 46%, although there has been a net survival improvement during the last decades, especially among young and mid-aged women [1,2].

The incidence of ovarian cancer has decreased during recent years in countries in which more women have used oral contraceptives for long periods; moreover, where new therapeutic strategies have been introduced (particularly for germ cell cancers) there has been a reduction in mortality rates [3,4]. The primary intervention is normally surgery, though even in early-stage disease many recommend adjuvant chemotherapy [5,6].

The high mortality rate of ovarian cancer is largely due to its late stage at presentation, partly related to the lack of early symptoms and effective screening methods [7,8]. To date, screening asymptomatic women without a genetic predisposition has not been proven to reduce mortality, and yet it does increase the risk of healthy women undergoing unnecessary surgical procedures [8], with the inevitable associated morbidity and risk of surgical mortality [9]. Hence, this position statement will examine the evidence regarding risk-reducing strategies.

2. Histological types and carcinogenic trajectories

Ovarian cancer types include:(1) epithelial ovarian carcinomas (EOCs) (90%), usually in postmenopausal women; (2) germ cell carcinomas (4%), more common in adolescents and women in their early 20s; (3) stromal carcinomas (teratomas, dysgerminomas and endodermal sinus tumors), diagnosed mostly at early stages; and (4) other primitive and metastatic malignant tumors, which are rarer. Epithelial ovarian carcinomas (EOCs) can arise not only from the ovarian surface but also from the fallopian tubes and the peritoneum [10-15]. This knowledge creates a new scenario for opportunistic bilateral salpingectomy to prevent ovarian cancer, while preserving the ovarian endocrine function [16-19]. This is important for premenopausal women since bilateral oophorectomy has been related to higher all-cause mortality and death rates due to ischemic heart disease and cancer [20].

Each histologic variety of ovarian cancer is associated with a different clinical natural history, epidemiologic factors and genetic and familial influences [12,21,22]. Although the precise causes of ovarian cancers are unknown, environmental, genetic, hormonal, and local genital factors have all been implicated. Some ovarian cancers cluster in families (hereditary

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ovarian cancer) and develop and progress earlier than sporadic (non-hereditary) tumors. Clinical and molecular studies suggest two different carcinogenic trajectories. Type I includes low-grade serous, clear cell, low-grade endometrioid, mucinous cancers and Brenner tumors, all of which are relatively stable from a genetic point of view. Type II includes high-grade epithelial serous, high-grade endometrioid and undifferentiated cancers and mixed mesodermal malignancies. These have a high genetic instability and a high p53 mutation prevalence [23]. They arise from extra-ovarian tissue, mostly the fallopian tubes [13,24].

Epithelial ovarian borderline tumors (EOBT) are of low malignant potential, are different from low-grade tumors and are typically diagnosed in young women [15,25]. EOBT tumors usually require less radical treatments than frankly malignant ovarian cancers, and usually have a favorable prognosis, although they may recur even 20 years after primary diagnosis. The majority of these tumors are mucinous and serous. However, prognosis cannot be predicted by their histopathology [26]. During the last decades, the incidence of EOBT has increased 2- to 5-fold, probably due to greater histopathological experience [27,28].

Pelvic inflammation may be associated with both borderline ovarian tumors and cancers, and this risk may increase for women who experience multiple inflammatory episodes [29,30].

3. Familial cancer

A family history of ovarian cancer (and related syndromes) is a well-recognized risk factor. Thus, the presence of an ovarian cancer in one first-degree relative increases women's lifetime risk by 5%; the risk increases up to 7% if there are 2 such relatives [31]. The risk is also high in families with hereditary breast and ovarian cancer syndromes in association with autosomal dominant mutations of the BRCA1 and BRCA2 genes (such syndromes are also associated with TP53 genes, but at a lesser frequency). However, other genes also seem to play a significant role (along with lifestyle factors) in the genesis of different subtypes of EOCs [32].

3.1. BRCA1 and BRCA2 gene mutations

BRCA1 and BRCA2 gene mutations increase ovarian and breast cancer risk, and also to a lesser degree the risk for fallopian tube, peritoneal, and pancreatic cancers. The risk of ovarian cancer is higher in BRCA1 carriers (two-fold) than in BRCA2 carriers [33]. Furthermore, women with fallopian tube cancer frequently have BRCA1 or BRCA2 gene mutations [34]. Some women with BRCA mutations have lower survival rates, and this has been related to a

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higher FIGO disease stage at diagnosis and more aggressive serous variants, suggesting that familial cancers are more aggressive than non-familial cancer types [35]. In contrast, the risk of endometrial cancer in families with BRCA gene mutations is nearly the same as that found in the general population without such mutations. Nonetheless, BRCA mutation carriers may also have a slightly increased risk of serous and/or serous-like endometrial carcinomas (but not endometrioid type) [36]. In some BRCA1 mutation carriers, the increased risk of endometrial cancer has been related to the use of tamoxifen [37]. Therefore, women considering salpingo-oophorectomy (e.g. those who are BRCA positive) should also envisage hysterectomy, especially if it is anticipated that they will take tamoxifen for a long period.

Preventive surgery should be individualized to the woman's specific circumstances, including her age and reproductive desires, and the presence of uterine pathology. Prophylactic oophorectomy (preferentially a salpingo-oophorectomy), which may be combined with hysterectomy, can be offered to women aged over 35 years who have completed childbearing. Preventive salpingo-oophorectomy is associated with an 80% reduction in the risk of ovarian, fallopian tube, or peritoneal cancer in BRCA1 or BRCA2 carriers and a 77% reduction in all-cause mortality [38]. However, intra-abdominal carcinomatosis of ovarian serous malignancies has been reported after bilateral salpingo-oophorectomy in women with BRCA mutations [39,40]. Despite this small risk, bilateral salpingo-oophorectomy remains the most cost-effective prophylactic intervention and reduces all-cause mortality [38,41,42]. This intervention can also prevent breast cancer in premenopausal women with BRCA2 mutations, although not those with BRCA1 mutations [43]. Premenopausal women with BRCA1 or BRCA2 mutations or with less frequent gene mutations, without prior breast cancer, undergoing oophorectomy should be advised to take menopausal hormone therapy (MHT) until the average age of natural menopause, since it does not appear to increase the risk of breast cancer [44-46]. A meta-analysis indicates that in these women and among those undergoing prophylactic salpingo-oophorectomy before the age of 40, MHT should be individualized and closely monitored [46]. This population may have an increased risk of endometrial cancer [36,47]. In light of this evidence, the option to include a hysterectomy as part of the surgical preventive intervention may be considered but must be balanced against the extra surgical morbidity.

Contraceptive interventions have been studied in women with BRCA gene mutations. Since many EOCs originate from fallopian tube lesions, the effect of tubal ligation and other contraceptive treatments has been studied though data are limited. In BRCA gene carriers,

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tubal ligation is associated with a non-significant reduction of fallopian tubal cancer while oral contraceptive use has a protective role [48].

3.2. Other gene mutations related to an increased risk of ovarian cancer

Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome (or Cowden disease) is characterized by thyroid problems (including cancer) and breast cancer. These women also have an increased risk of serous EOC, which is related to gene mutations [49,50]. Women with hereditary nonpolyposis colon cancer (Lynch syndrome) also have an increased risk of endometrial cancer and (to a lesser extent) ovarian cancer. Women with Lynch syndrome have a lifetime risk of ovarian cancer of about 10% and they represent up to 1% of all EOCs [51,52].

Peutz-Jeghers syndrome usually affects teenagers; they have a high risk of cancer at different digestive sites as well as of epithelial or sex cord ovarian cancers. This syndrome is related with the STK11 gene mutation [52].

The preventive management of gynecological cancer risk in all these gene-mutated syndromes (although risks are less than with BRCA mutations) includes bilateral salpingo-oophorectomy. In women with Lynch syndrome, hysterectomy should be also considered because of the increased risk of endometrial cancer.

4. Surgical strategies to reduce ovarian cancer risk

Prophylactic bilateral salpingo-oophorectomy has been used at the time of hysterectomy among postmenopausal women with benign conditions, although its use in premenopausal women seems a matter of controversy. In the premenopausal population, there has been a trend to change bilateral salpingo-oophorectomy to bilateral salpingectomy during the last decade [16,17,53], in order to preserve ovarian function yet eliminate fallopian tubes as the source of the initial EOC. It seems that in women with an average risk of ovarian cancer, ovary preservation may have general health benefits, including the reduction of future cardiovascular risk, osteoporosis, sexual dysfunction, cognitive function and mental health, and impaired quality of life [20,54].

Fallopian tubal ligation and hysterectomy (if performed before age 35) reduce the risk of EOC, particularly non-serous types [55,56]. An Australian Cancer Study, a Danish register-based case-control study, and the Million Women Study reported that tubal ligation has different preventive effects according to histologic types, the protection being greater for high-

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risk serous, endometrioid and clear cell carcinomas, while results are conflicting regarding mucinous carcinomas [16,57,58].

The effect of salpingectomy on ovarian cancer risk has been compared with that provided by tubal ligation. Madsen et al [16] and Falconer et al [17] reported that salpingectomy reduced EOC in the Danish register-based case-control study and in a national US population-based study, respectively. The results suggest that opportunistic bilateral salpingectomy should be recommended when women are treated by hysterectomy for benign conditions and among those seeking sterilization [18,19]. This approach means the preservation of ovarian function with the prevention of the all-cause mortality and death rate due to ischemic heart disease and cancer, associated with oophorectomy [20]

Hysterectomy alone due to benign conditions in young women, with conservation of the fallopian tubes and the ovaries, may also reduce the risk of ovarian cancer [56,58].

5. Hormonal interventions and ovarian cancer risk

Combined oral contraceptives (COC) reduce the risk of EOC. The use of oral contraceptives is associated with a reduction in ovarian cancer risk in the general population [59], probably related to anovulation (reduction of the risk of implantation of fallopian tube cancer cells). A meta-analysis of case-control and cohort studies reported a significant reduction in ovarian cancer risk whenever users are compared with never users. In addition, when use is for 10 or more years there is a reduction of more than 50% in the incidence [60]. However, COCs do not seem to affect the incidence of mucinous tumors [61]. On the other hand, the use of progestogen-only contraceptive pills does not seem to provide protection against ovarian cancer risk [62]. Despite this, the levonorgestrel-releasing intrauterine system decreases the risk of mucinous, endometrioid and serous ovarian carcinomas [63].

The protective effect of COC is closely related to the dose of estrogen and treatment duration, although there is no accumulative effect of estrogen intake [62], and the protective effect is not reduced with increasing age [64]. COC use before the first full-term pregnancy has a protective effect on the risk of EOC. A case-control study of invasive EOC in parous women aged 40 or more reported a 9% risk reduction in those who used combined contraceptives before the first birth, suggesting a prolonged protective effect after cessation of COC use [65]. Combined hormone contraceptive use also has a significant inverse association with BRCA-related ovarian cancer risk, and the effect is similar when BRCA1 or BRCA2 mutation carrying women are analyzed separately [66].

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The incidence of EOC has been associated with the use of menopausal hormone therapy. The worldwide reduction in the prevalence of ovarian cancer during the last decade has been linked with the decline in MHT use [67,68], although the causality of this association has been strongly refuted [59,69,70]. No adverse effects have been shown with MHT use after diagnosis and treatment for ovarian cancer [71]. However, there are concerns for women with advanced endometrioid adenocarcinomas who may have residual disease that is hormone-sensitive. While there is a lack of data regarding the use of MHT post-treatment for germ cell tumors, it is typically thought to be safe. Similarly, there are no data on the safety of MHT after treatment for granulosa cell tumors, but it is generally avoided as these tumors are frequently hormonally active [72].

6. Non-hormonal interventions

Non-steroidal anti-inflammatory drugs (NSAIDs) and some analgesics may have chemopreventive actions against cancer from different organs. Low-dose aspirin (150 mg/day for ≥ 5 years) may reduce the risk of EOC: with regard to histological types, the strongest inverse associations were seen for mucinous and endometrioid tumors [73]. The African American Cancer Epidemiology Study on EOC risk analyzed the effect of aspirin, non-aspirin NSAIDs and acetaminophen on ovarian cancer risk and found that it was significant for NSAIDs (aspirin and non-aspirin) while acetaminophen had no protective effect. It is likely that ovarian follicle rupture during ovulation releases fluid containing prostaglandins and other compounds that induce inflammation, which can potentially be neutralized by NSAIDs [74]. Therefore, small doses of NSAIDs may be a preventive intervention for women at high risk of ovarian cancer but more research is required.

7. Diet and lifestyle

Studies analyzing the association between dietary types or contents, alcohol consumption, and coffee or tea consumption have not provided any recommendation to prevent ovarian cancer. The effect of recreational physical activity on ovarian cancer risk is inconclusive or controversial. A meta-analysis reported a 12% increase in EOC risk for obese women (>30 kg/m^2), after adjusting for different confounding factors such as MHT use [75]. Furthermore, another meta-analysis of prospective studies reported a non-linear increase in ovarian cancer for each 5 units of BMI increase, this rise starting with a BMI of 28 kg/m^2 and above. In addition, there was no association between ovarian cancer and weight gain, hip

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circumference or waist–hip ratio [76]. A recent study among African American women pointed out that ovarian cancer risk is significantly elevated in women with BMI ≥ 40 kg/m^2 as compared with those with a BMI <25, and there is an association between this cancer risk and weight gain after age 18 comparing the highest versus the lowest quartile. In postmenopausal women (MHT users and non-users) ovarian cancer risk increased by 15% per 5 kg/m^2 increase of BMI, or 6% per 5 kg of weight gain [77]. For each 5 kg increase in adult weight, ovarian cancer risk increases in postmenopausal women, both in users and non-users of MHT [78]. In addition, in postmenopausal women the risk is similar among MHT users and non-users. It is important to note that obesity does not seem to increase the risk of the most aggressive (or lethal) cancers, and that associations are similar in MHT users and non-users [79]. These results suggest the importance of avoiding obesity in young women and preventing weight gain.

Cigarette smoking has been associated with certain histologic subtypes of ovarian cancer [80]. Women who smoked for more than 20 years had 3 times the risk of developing borderline EOCs as compared with never smokers, and there was an almost significant relation for mucinous tumors. In addition, there was also a significant dose–response effect with smoking intensity and duration for both borderline and serous tumors [81,82]. Another recent study reported that smoking is associated with an increased risk of mucinous cancers, and a decreased risk for clear cell cancers [83]. Therefore, on these grounds alone, it is recommended that tobacco consumption is reduced or eliminated.

8. Summary

- Opportunistic bilateral salpingectomy may prevent ovarian cancer. Bilateral salpingectomy should be preferred to tubal ligation, and should be recommended in cases of hysterectomy for benign conditions.
- Combined but not progestogen-only contraceptive medication reduces the risk of ovarian cancer.
- Menopausal hormone therapy should be individualized in oophorectomized BRCA gene mutation carriers or among those with other genetic-related increased ovarian cancer risk.
- NSAIDs, particularly aspirin, may reduce the risk of ovarian cancer but more research is required.

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- Being overweight or obese increases the risk of ovarian cancer. There is no evidence that any particular diet reduces the risk of ovarian cancer.

Provenance and peer review

This article is an EMAS position statement and was not externally peer reviewed.

Contributors

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