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No. 344-Opportunistic Salpingectomy and Other Methods of Risk Reduction for Ovarian/Fallopian Tube/Peritoneal Cancer in the General Population

This Clinical Practice Guideline has been prepared by the Society of Gynecologic Oncology of Canada (GOC) Guidelines Committee and reviewed by the Society of Obstetricians and Gynaecologists of Canada's Clinical Practice—Gynaecology, Medico-Legal, and Guideline Management and Oversight committees and approved by the Executive and Board of the Society of GOC and by the Board of the SOGC.

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Key Words: Serous ovarian neoplasms, fallopian tube neoplasms, salpingectomy, primary prevention

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Abstract

Objective: This guideline reviews the potential benefits of opportunistic salpingectomy to prevent the development of high grade serous cancers (HGSC) of the ovary/fallopian tube/peritoneum based on current evidence supporting the fallopian tube origin of disease.

Intended Users: Gynaecologists, obstetricians, family doctors, registered nurses, nurse practitioners, residents, and health care providers.

Target Population: Adult women (18 and older):

- Who have completed childbearing, and
- Who will undergo a gynaecologic procedure such as hysterectomy or permanent sterilization with the intention of leaving the ovaries in situ.

Options: Women considering hysterectomy who wish to retain their ovaries in situ have traditionally also retained their fallopian tubes. In addition, women undergoing permanent surgical sterilization have usually undergone tubal ligation using various methods rather than undergoing surgical removal of the entire fallopian tube.

Evidence: For the sections "Evidence Supporting the Hypothesis That HGSC Originates in the Fallopian Tube" and "Current Literature on the Effects and Safety of Opportunistic Salpingectomy," relevant studies were searched in PubMed, Medline, and the Cochrane Systematic Reviews using the following terms, either alone or in combination, with the search limited to English language materials: "high grade serous cancers ovary," "fallopian tube," "peritoneum," "opportunistic salpingectomy," "epithelial ovarian cancers," "origin," "tubal carcinoma in situ," "BRCA mutation," "prophylactic salpingectomy," "inflammation," "clear cell," and "endometrioid." The initial search was performed in March 2015 with a final literature search in March 2016. Relevant evidence was selected for inclusion in the following order: meta-analyses, systematic

reviews, guidelines, randomized controlled trials, prospective cohort studies, observational studies, non-systematic reviews, case series, and reports. The total number of studies identified was 458, and 56 studies were included in this review. For the section "Other Factors Influencing the Risk of Developing "Ovarian" Cancers" a general Medline search was carried out using the terms "ovarian neoplasm" and "prevention." The search included papers published from December 2005 to March 2016. Meta-analyses were preferentially selected except where no such review was found. Additional searches for each subheading were also conducted (e.g., "ovarian neoplasm" and "tubal ligation.") Additional significant articles were identified through cross-referencing the identified reviews. For the search for "ovarian neoplasm" and "prevention," 10 meta-analyses were identified. For the search for "ovarian neoplasm" and "tubal ligation," an additional 4 meta-analyses were identified.

Validation Methods: The content and recommendations were drafted and agreed on by the principal authors. The Executive and Board of the Society of Gynecologic Oncology of Canada reviewed the content and submitted comments for consideration, and the Board of the SOGC approved the final draft for publication. The quality of evidence was rated using the criteria described in the Grading of Recommendations Assessment, Development and Evaluation methodology framework (Table 1). The interpretation of strong and weak recommendations is described in Table 2. The summary of findings is available on request.

Benefits, Harms, and/or Costs: The addition of opportunistic salpingectomy to a planned hysterectomy or permanent sterilization did not increase rates of hospital readmission (OR 0.91, 95% CI 0.75 to 1.10 and OR 0.8, 95% CI 0.56 to 1.21, respectively) or blood transfusions (OR 0.86, 95% CI 0.67 to 1.10 and OR 0.75, 95% CI 0.32 to 1.73, respectively) but did increase the overall operating time (by 16 minutes and 10 minutes, respectively) in a retrospective review of 43 931 women. The risk of repeat surgery for tubal pathology among women with retained fallopian tubes after hysterectomy was at least doubled (OR 2.13, 95% CI 1.88 to 2.42 in a population-based study of 170 000 women). If general gynaecologists were to consider removal of fallopian tubes at the time of every hysterectomy and sterilization procedure with referral of all patients with HGSC for hereditary cancer counselling and genetic testing, experts project a potential reduction in the rate of HGSC by 40% over the next 20 years.

Guideline Update: Evidence will be reviewed 5 years after publication to decide whether all or part of the guideline should be updated. However, if important new evidence is published prior to the 5-year cycle, the review process may be accelerated for a more rapid update of some recommendations.

Sponsors: This guideline was developed with resources funded by the Society of Gynecologic Oncology of Canada and SOGC.

Summary Statements

1. High-grade serous cancers of the ovary/fallopian tube/primary peritoneum account for approximately 70% of all epithelial cancers and differ from other epithelial cancers in their presentation, most prevalent stage, response to treatments, overall prognosis, and recurrence rates (High).
2. Fallopian tube cancers, previously believed to be quite rare, are high-grade serous cancers approximately 90% of the time and have identified precursor lesions (serous tubal intraepithelial carcinomas), whereas precursor lesions have not been identified on the epithelial surface of the ovary (High).
3. The recent change to the International Federation of Gynecology and Obstetrics staging system for high-grade serous cancers in 2014 included ovary, fallopian tube, and primary peritoneum together as primary sites of disease, reflecting the difficulty in distinguishing the location in which the cancer developed (High).
4. Prophylactic bilateral salpingo-oophorectomy can reduce the risk of high-grade serous cancers by 80% to 90% for breast cancer mutation carriers (High).
5. In women with breast cancer mutations, 5% to 6% of fallopian tubes from prophylactic salpingo-oophorectomies have serous tubal intraepithelial carcinomas present (High).
6. Serous tubal intraepithelial carcinomas are found most commonly at the fimbriated end of the fallopian tube and have p53 mutation changes identical to associated cancers (High).
7. Clear cell and endometrioid carcinomas are now believed to originate from endometriotic lesions deposited within the pelvis and around the ovary (High).
8. Oral contraceptive pill use effectively reduces the lifetime risk of developing an "ovarian" cancer by 50% when taken for more than 10 years (High).
9. Tubal ligation reduces the risk of endometrioid cancer by 52% and clear cell cancer by 48%, presumably by blocking retrograde menstruation and preventing endometriotic deposits within the pelvis. However, tubal ligation reduces the risk of developing high-grade serous cancers by only 19%, supporting the theory that these cancers arise within the distal end of the remaining fallopian tube (Moderate).
10. The strategy with greatest potential for risk reduction is bilateral salpingo-oophorectomy, which reduced the mortality rate from "ovarian" cancer in the Nurses' Health Study by 94%; however, the overall risk of death from any cause following bilateral salpingo-oophorectomy increased by 12%, reflecting the protective effect of estrogen in preventing cardiovascular disease before age 50 (High).
11. The effect of diet and obesity on "ovarian" cancer risk is currently unclear and requires further research (Low).
12. The role of metformin in the primary prevention of "ovarian" cancer needs further research for clarification (Low).

ABBREVIATIONS

ASA	acetylsalicylic acid
BRCA	breast cancer
BTL	bilateral tubal ligation
CI	confidence interval
CS	Caesarean section
EOC	epithelial ovarian cancers
FIGO	International Federation of Gynecology and Obstetrics
HGSC	high-grade serous cancers
HR	hazard ratio
IVF	in vitro fertilization
OCP	oral contraceptive pill
OR	odds ratio
RR	relative risk
SEE-FIM	sectioning and extensively examining the fimbria
STIC	serous tubal intraepithelial carcinomas

13. There is insufficient evidence to link the use of talc-containing products with “ovarian” cancer (Moderate).
14. Acetylsalicylic acid has been shown to reduce the risk of “ovarian” cancer, but the effect of non-acetylsalicylic acid, non-steroidal anti-inflammatory drugs and acetaminophen is unclear (Moderate).
15. There has been no effective screening protocol to date that can decrease mortality from “ovarian” cancer in the general population (Moderate).
16. There is no established link between the use of “ovulation stimulating drugs” and “ovarian” cancer (Moderate).
17. Treating endometriosis may reduce the risk of “ovarian” cancer (Low).
18. Performing opportunistic salpingectomy at the time of hysterectomy for benign gynaecologic disorders does not increase complication rates, length of hospital stay, or overall recovery time but does lead to a minor increase in surgical time (Moderate).
19. Retaining the fallopian tubes at the time of hysterectomy increases the risk of subsequent reoperation for tubal pathology (Moderate).
20. Population-based studies are required to evaluate whether opportunistic salpingectomy can reduce the incidence of high-grade serous cancers (Moderate).

Recommendations

1. The use of an oral contraceptive pill reduces the risk of users developing high-grade serous cancers and should be discussed when counselling women on contraceptive use (Strong, High).
2. When considering permanent contraception, tubal ligation is shown to have the additional benefit of reducing the risk of developing high-grade serous cancers. However, the fact that the complete removal of the fallopian tube may provide additional benefit should be discussed (Strong, High).
3. Removal of the ovaries in premenopausal women may increase the risk of cardiovascular disease and is not recommended without clinical indication (Strong, High).
4. Population-based screening should not be encouraged as a method of “ovarian” cancer risk reduction (Strong, High).
5. In considering hysterectomy with the ovaries remaining in situ, the fact that the removal of easily accessible fallopian tubes may reduce the risk of developing high-grade serous cancers without additional procedural risk, and is recommended, should be discussed (Strong, Moderate).
6. Prospective population-based surgical databases should be kept to monitor the effect of opportunistic salpingectomy on overall morbidity and mortality and especially the rates of high-grade serous cancers (Strong, Moderate).

INTRODUCTION

Ovarian cancer is the 5th leading cause of cancer-related deaths in women in Canada, and each year there are approximately 2800 new cases and 1750 deaths.[1] The 5-year overall survival rate remains poor at approximately 40%.[2] However, we have come to realize that "ovarian" cancer is a spectrum of diseases with different etiologies. Through extensive pathologic examination of HGSC of the ovary, it has been proposed that most of these cancers actually originate within the fallopian tube.[3] If this is the case, opportunistic bilateral salpingectomy should be considered as a preventative measure against the development of HGSC of the fallopian tube/ovary/primary peritoneum.

Several national and international gynaecologic societies (Society of Gynecologic Oncology of Canada,[4] the American Congress of Obstetricians and Gynecologists,[5] Society of Gynecologic Oncology,[6] and Kommission Ovar[7]) have released expert opinion statements that recommend physicians discuss the risks and benefits of opportunistic salpingectomy with patients undergoing a hysterectomy or irreversible surgical contraception because of strong evidence for potential cancer prevention. National studies must be conducted to prospectively collect data that will evaluate the long-term effects of opportunistic salpingectomy.

Evidence Supporting the Hypothesis That HGSC Originates in the Fallopian Tube

Pathophysiology of HGSC

HGSC are the most prevalent of the EOC and account for 70% of EOC.[8] The other histologic subtypes of EOC, including endometrioid cancer, clear cell cancer, mucinous cancer, and low grade serous cancers, have very distinct presentations.[3,8–10] These subtypes differ from HGSC in that they present at an earlier stage at diagnosis and have a varied response to current treatments, differing overall prognosis, and recurrence rates. They also differ in their proposed origins of disease.

HGSC are distinct from the other classified EOC in that they almost all have p53 mutations, likely one of the initial mutations starting the disease process.[11] They are also associated with Ki-67 mutations. BRCA mutations, either somatic or germline, occur within 30% to 50% of these tumours.[12–15] The combination of p53 mutation and BRCA dysfunction leads to severe DNA repair malfunction, making HGSC extremely responsive to chemotherapy. However, the DNA repair malfunction also leads to rapid mutations that allow the disease to develop resistance to these treatments, causing frequent recurrence of disease.

Previous hypotheses related to primary fallopian tube cancer

Previous hypotheses concerning the origin of HGSC included the incessant ovulation theory and the excessive

Table 1. Key to Grading of Recommendations, Assessment, Development and Evaluation (GRADE)

Strength of the recommendation	Definition
Strong	Highly confident of the balance between desirable and undesirable consequences (i.e., desirable consequences outweigh the undesirable consequences or undesirable consequences outweigh the desirable consequences).
Weak[a]	Less confident of the balance between desirable and undesirable consequences.
Quality level of a body of evidence	Definition
High|++++	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate|+++0	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low|++00	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low|+000	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Examples:

Strong, Moderate|+++0: Strong recommendation, moderate quality of evidence

Weak, Low|++00: Weak recommendation, low quality of evidence

Taken from: Schünemann H, Brozek J, Guyatt G, Oxman A, editors. The GRADE Handbook. GRADE Working Group; 2013. Available at: http://gdt.guidelinedevelopment.org/app/handbook/handbook.html. Accessed on January 2, 2017.

[a]Weak recommendations should not be misinterpreted as weak evidence or uncertainty of the recommendation.

Table 2. Judgement and interpretation of strong and conditional recommendations

Judgement/interpretation	Strong recommendation "We recommend…"	Conditional recommendation "We suggest…"
Judgement by guideline panel	It is clear to the panel that the net desirable consequences of a strategy outweighed the consequences of the alternative strategy.	It is less clear to the panel whether the net desirable consequences of a strategy outweighed the alternative strategy.
Implications for patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Implications for clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual to arrive at a management decision consistent with his or her values and preferences.
Implications for policy makers	The recommendation can be adopted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

Taken from: Schünemann H, Brozek J, Guyatt G, Oxman A, editors. The GRADE Handbook. GRADE Working Group; 2013. Available at: http://gdt.guidelinedevelopment.org/app/handbook/handbook.html. Accessed on January 2, 2017.

gonadotropin theory. The incessant ovulation theory proposes that a woman's lifetime number of ovulatory cycles is positively associated with "ovarian" cancer risk due to repetitive damage and repair of the ovarian surface epithelium.[16] The excessive gonadotropin theory postulates that high levels of gonadotropins and estrogen lead to stimulation and proliferation of the ovarian surface epithelium.[17] The validity of these hypotheses has never been substantiated with identifiable pre-invasive lesions in surgically removed ovaries.

Primary fallopian tube cancer was previously considered to be a very rare gynaecologic cancer. With fewer than 2500 cases reported prior to 2008, it was believed to account for only 1% of female genital tract malignancies.[18] This was due to the very strict diagnostic definition of a primary fallopian tube cancer, which required the site of origin to have the largest tumour burden.[19,20] These cancers frequently presented as a unilateral fallopian tube tumour with occluded fimbriae preventing the spread of the cancer throughout the abdomen. The most prevalent histology of a cancer arising within the fallopian tube is high-grade serous, approaching almost 90% of all cases. Precursor lesions were identified and labelled "tubal carcinoma in situ." These precursors are often noted in the fimbria adjacent to invasive cancers, suggesting a direct histologic transition.[21] The previous FIGO staging system classified fallopian tube cancers as a distinct disease and assumed that HGSC were arising from the ovary. The most recent FIGO staging system reflects the findings of HGSC precursor lesions in the fallopian tube and genetic mutations and deals with ovarian, fallopian tube, and primary peritoneal cancers together as one entity.[22] Guidelines for assigning the primary site of HGSC based on careful macroscopic and histologic assessment have been proposed.[23]

BRCA mutation carriers and evidence obtained from prophylactic salpingo-oophorectomies

The lifetime risk of developing HGSC of the ovary, fallopian tube, or peritoneum approaches 30% for BRCA2 mutation carriers and up to 60% for BRCA1 mutation carriers.[15] In this patient population, prophylactic salpingo-oophorectomy can reduce this risk by 80% to 90%.[24,25] At the time of prophylactic surgery in this patient population, HGSC are identified at a rate of 5% to 15%.[26–28] On pathologic examination, precursor lesions are found to arise predominantly in the distal fallopian tube and not within the ovary. In addition, premalignant epithelial changes known as STIC are noted to arise in the distal fallopian tube in an additional 5% to 6% of cases.[26,29–31]

The findings of incidental HGSC and STIC led to the development of the SEE-FIM protocol.[32] This pathology protocol mandates a more extensive examination of the fallopian tubes. With the application of this new protocol, STIC are found at an increasing frequency (8%) within the prophylactically removed tubes.[33] Further study of these STIC has revealed that they, too, have p53 and Ki-67 mutations, similar to HGSC.[32,33] Data have been collected showing that women who have had only their ovaries removed at the time of prophylactic surgery have a greater risk of developing primary peritoneal HGSC (11%)[28] than do women who have also had the fallopian tubes removed (5%).[34]

Evidence that the majority of HGSC arise within the fallopian tube in the general population

Application of the SEE-FIM protocol to the pathologic assessment of all extrauterine cases of HGSC has resulted in the identification of STIC in 40% to 60% of women with an initial diagnosis of primary ovarian[35–37] or peritoneal cancer.[38,39] These premalignant lesions were found within

the fimbriated end of the fallopian tube and had p53 mutation changes identical to mutation changes found within adjacent cancers.[35] STIC have also been shown to have DNA gene copy number changes that are similar to the adjacent invasive HGSC, suggesting a clonal relationship between the 2 disease processes.[36] The discovery of STIC within the fallopian tube has promoted the search for precursor lesions. These have now been described as "p53 signatures," foci of strong p53 immuno-positivity in otherwise benign-appearing fallopian tube epithelium.[40] Additional studies have found a shared p53 mutation between the p53 signature and an adjacent STIC lesion,[40]and p53 signatures within the fallopian tubes of BRCA mutation carriers but not on the adjacent ovaries.[41] It is biologically plausible that the fimbriated end of the fallopian tube is the primary source of HGSC. First, the surface area of the fimbriated end is vast in comparison with the remaining fallopian tube and ovarian surface, and as such, it is at a proportionately higher risk of developing a cancer. Second, the fallopian tube is composed of Müllerian cells, which are inclined to give rise to serous type cancers. Finally, the fallopian tube is bathed in a pro-inflammatory environment, discussed in the following section, which could promote the development of the p53 signatures and mutations.[42]

Environment of inflammation within the fallopian tube

With every ovulation a pro-inflammatory environment is established within the distal end of the fallopian tube. Extensive infiltration of leukocytes, inflammatory cytokines, and reactive oxygen species have been identified as the distal end of the tube is bathed in the follicular fluid released at ovulation.[42–44] Continuous exposure to the ovulatory environment has been proposed to cause the DNA damage and p53 mutations identified within the fimbriated end of the fallopian tube that leads to the development of STIC and invasive HGSC.[42] Factors known to reduce the risk of HGSC, such as oral contraceptive use, increased parity, and breastfeeding, reduce the incidence of ovulation and thereby decrease the exposure of the fallopian tube to these inflammatory factors.

Menstruation has also been found to contribute to inflammation in the fallopian tube. Retrograde menstruation with iron-rich blood flows through the fallopian tube in every menstrual cycle, and iron-induced oxidative stress has been proven to induce cancerous changes within cells.[45] This passage of menstrual blood also carries cytokines and other irritants such as talc[44] and sexually transmitted infections,[46] which have been linked to "ovarian" cancer.[47,48] Methods of sterilization that block the fallopian tube and prevent the passage of irritants through the tube are strongly associated with a decreased risk of developing "ovarian" cancer.[49]

The fallopian tube and non-serous subtypes of gynaecologic malignancy

Clear cell carcinoma and endometrioid carcinoma are other forms of EOC that have been believed to originate from the ovary. However, these cancers are now believed to originate from endometriotic lesions deposited around the ovary.[50,51] Endometriosis arises from implantation of endometrial cells outside the uterus. It is also highly inflammatory, inducing cytokine and prostaglandin release in the surrounding tissue exposed to the disease.[52] The clear cell and endometrioid cancers that develop within endometriosis often have shared mutations. Tubal sterilization has been shown to significantly decrease the risk of developing clear cell and endometrioid "ovarian" cancer, presumably by blocking retrograde menstruation.[49]

Summary Statements

1. High-grade serous cancers of the ovary/fallopian tube/primary peritoneum account for approximately 70% of all epithelial cancers and differ from other epithelial cancers in their presentation, most prevalent stage, response to treatments, overall prognosis, and recurrence rates (High).
2. Fallopian tube cancers, previously believed to be quite rare, are high-grade serous cancers approximately 90% of the time and have identified precursor lesions (serous tubal intraepithelial carcinomas), whereas precursor lesions have not been identified on the epithelial surface of the ovary (High).
3. The recent change to the International Federation of Gynecology and Obstetrics staging system for high-grade serous cancers in 2014 included ovary, fallopian tube, and primary peritoneum together as primary sites of disease, reflecting the difficulty in distinguishing the location in which the cancer developed (High).
4. Prophylactic bilateral salpingo-oophorectomy can reduce the risk of high-grade serous cancers by 80% to 90% for breast cancer mutation carriers (High).
5. In women with breast cancer mutations, 5% to 6% of fallopian tubes from prophylactic salpingo-oophorectomies have serous tubal intraepithelial carcinomas present (High).
6. Serous tubal intraepithelial carcinomas are found most commonly at the fimbriated end of the fallopian tube and have p53 mutation changes identical to associated cancers (High).

7. Clear cell and endometrioid carcinomas are now believed to originate from endometriotic lesions deposited within the pelvis and around the ovary (High).

Other Factors Influencing the Risk of Developing "Ovarian" Cancers

OCP

The relationship between oral contraceptive use and "ovarian" cancer risk has been extensively reviewed. The OCP decreases the risk of "ovarian" cancer proportionate to its length of use. The average risk reduction per year of use is 5% to 8%.[53] A recent meta-analysis of 55 studies demonstrated a lifetime reduction in "ovarian" cancer risk of 50% for a woman taking the OCP for more than 10 years.[54]

Faber et al.[53] investigated a possible relationship between hormone dose in OCP users and risk of "ovarian" cancer. The only clear conclusion from their case control review was that progestin-only formulations do not reduce "ovarian" cancer risk. They did not find a relationship between the dose of estrogen or progestin and the degree of risk reduction. They concluded that any combined OCP preparation is sufficient to reduce cancer risk provided that it inhibits ovulation.

The relationship between OCP use and reduction in risk of "ovarian" cancer with specific histology has not been as extensively reviewed.[53] However, a prospective study by Yang et al.[55] suggests that OCP use decreases the risk of serous and endometrioid "ovarian cancers" but increases the risk of mucinous "ovarian" cancers.

Tubal ligation

Tubal ligation has for some time been known to decrease the risk of developing "ovarian" cancer. More recent analyses have been able to quantify the degree of risk reduction according to different histologic subtypes of "ovarian" cancer.[49,56,57] A meta-analysis of 13 studies showed that tubal ligation was associated with a RR of 0.4 for endometrioid cancers and an RR of 0.73 for serous cancers but that it was not associated with a reduction in mucinous cancers.[56] A pooled analysis by Sieh et al.[49] demonstrated that the risk reduction with tubal ligation was 52% for endometrioid cancer (OR 0.48, 95% CI 0.40 to 0.59; $P < 0.001$); 48% for clear cell cancer (OR 0.52, 95% CI 0.40 to 0.67; $P < 0.001$); and 32% for invasive mucinous cancer (OR 0.68, 95% CI 0.52 to 0.89; $P = 0.005$). The risk of developing invasive serous "ovarian" cancer was only reduced by 19% (OR 0.81, 95% CI 0.74 to 0.89; $P < 0.001$). No association was demonstrated between tubal ligation and risk of borderline mucinous and borderline serous tumours. These investigators accounted for parity and use of OCP in their analysis.

The relationship between risk reduction and histologic subtype is consistent with current theories on the differing pathogenesis of various types of "ovarian" cancer. The decreased risk of endometrioid and clear cell cancers after tubal ligation supports the theory that these cancers originate from exfoliated endometrial cells. Conversely, HGSC appear to arise predominantly in the distal tube. Therefore, to substantially reduce the risk of invasive serous cancer, the distal tube must be ablated or removed.

Bilateral salpingo-oophorectomy at the time of hysterectomy

Opportunistic oophorectomy at the time of hysterectomy does contribute to "ovarian" cancer risk reduction, but it also leads to an increase in all-cause mortality.[58] The Nurses' Health Study found that the rate of death from "ovarian" cancer after hysterectomy and conservation of the ovaries was only 0.03%. At the same time, all-cause mortality and other cancer-related deaths increased in women who underwent bilateral salpingo-oophorectomy at the time of hysterectomy.[58] Even though the rate of "ovarian" cancer-related death was reduced by 94% (HR 0.06, 95% CI 0.02 to 0.21), the risk of death from any cause was increased by 12% (HR 1.12, 95% CI 1.03 to 1.21). The Nurses' Health Study found that women who underwent bilateral oophorectomy before 50 and who never used estrogen replacement therapy had a significantly increased risk of dying from coronary artery disease (HR 1.98, 95% CI 1.18 to 3.32). A meta-analysis of observational studies found that oophorectomy doubled the risk of cardiovascular disease (RR 2.62, 95% CI 2.05 to 3.35).[59] Stroke risk is also increased in women who undergo oophorectomy and who do not then take estrogen therapy; in the Nurses' Health Study, the risk was almost doubled (HR 1.85, 95% CI 1.09 to 3.16).[58]

We do not recommend performing unilateral oophorectomy at the time of hysterectomy, although this can also decrease the risk of "ovarian" cancer. The risk reduction is not as significant as with bilateral salpingo-oophorectomy, and women who elect to have conservation of 1 ovary risk requiring repeat surgery for a variety of indications.[57]

Diet and obesity

The influence of diet on the risk of "ovarian" cancer is controversial. A recently reported systematic review of prospective studies with over 200 "ovarian" cancer cases (n = 24) found that total, animal, and dairy fat and nitrates increased the risk of "ovarian" cancer. Red meat intake

did not appear to increase "ovarian" cancer risk. Vegetables and in particular isoflavones and flavonoids were associated with a lower risk of "ovarian" cancer.[60]

Recently Merritt et al.[61] found evidence that a higher intake of omega-3 may reduce the risk of EOC, whereas a higher intake of trans fat may increase the risk of EOC. A case control study of 1000 individuals in China found that increased consumption of preserved foods was associated with an OR for developing EOC of 1.78 (95% CI 1.35 to 2.34).[62] The NIH-AARP Diet and Health Study in the United States found that a "high" intake of animal sources of nitrite increased "ovarian" cancer risk by 34% (95% CI 1.05 to 1.69).[63]

A 2007 meta-analysis of 24 studies found an OR of developing EOC of 1.3 (95% CI 1.1 to 1.5) in obese (BMI >30 kg/m^2) versus non-obese women.[64] This meta-analysis found no relationship between obesity and specific subtypes of "ovarian" cancer. A subsequent review of 15 case control studies found that obesity increased the risk of borderline serous, invasive mucinous, and invasive endometrioid "ovarian" cancer.[65] There was no association found between obesity and invasive serous "ovarian" cancer. Results were expressed in OR per 5 kg/m^2 increase in BMI. The most significant association between obesity and invasive cancer was found with grade 1 and 2 endometrioid cancers (OR [per 5 kg/m^2 increase] 1.25, $P \leq 0.001$). Obesity and nutritional status have been found to be associated with worse survival outcomes in women being treated for "ovarian" cancer.[66]

Metformin

Metformin (1,1-dimethylbiguanide) is a commonly used anti-hyperglycemic agent. Epidemiologic studies have revealed that metformin lowers cancer risk and improves cancer outcomes.[67] It does so by both direct and indirect anti-tumourigenic activity. A direct effect is achieved by its ability to inhibit mechanistic target of rapamycin-mediated cell proliferation. The indirect effect is achieved by blockage of hepatic gluconeogenesis. This results in lower circulating glucose and insulin levels, which in turn decrease growth factor-mediated tumour cell proliferation.[67] Clinical trials examining both the cancer prevention and the cancer treatment benefits of this agent are in progress.[68] A meta-analysis of 4 studies suggested that metformin decreases "ovarian" cancer risk (pooled OR 0.57, 95% CI 0.16 to 1.99).[69]

Products containing talc

Talcum powder is a moisture-absorbing mineral composed of magnesium silicate. It is commonly found in hygienic genital powders. Its use has been implicated as a cause of "ovarian" cancer for decades. A case control study comparing 8525 cases and 9859 controls found a small increased risk of EOC with talc use (OR 1.24, 95% CI 1.15 to 1.33).[70] Several reviews have concluded that the weak statistical association and the absence of a gradient effect argue against talc having a causal role.[71,72] The most recent review of association between talcum powder use and "ovarian" cancer was an analysis of prospectively collected data from the Women's Health Initiative Observational Study. In this study, talcum powder "ever use," "duration of use," and "modes of application" were prospectively recorded from 1993 to 1998 by a cohort of over 90 000 women. After exclusion of women who had undergone bilateral oophorectomy and/or who had missing data, 61 576 participants remained for review. The OR for developing "ovarian" cancer with "ever use" versus "never use" of talc was 1.06 (95% CI 0.87 to 1.28). Mode of application (i.e., direct application to the genitalia, use of sanitary napkins, or use of a diaphragm) did not influence the risk of developing "ovarian" cancer. Most importantly, duration of use was not associated with an increased risk of "ovarian" cancer. Women reporting durations of use over 10 years had an HR of invasive serous cancer of 0.96 (95% CI 0.88 to 1.53).[73]

Effect of acetylsalicylic acid (ASA), non-steroidal anti-inflammatory drugs, and acetaminophen on "ovarian" cancer risk

ASA has been shown to reduce the risk of "ovarian" cancer.[74] In a meta-analysis of 12 population-based case control studies that included 7776 cases and 11 843 controls, ASA use was associated with a reduced risk of "ovarian" cancer (OR 0.91, 95% CI 0.84 to 0.99).[75] Among daily ASA users, the OR was 0.80 (95% CI 0.67 to 0.96). Furthermore, among 3 studies that specifically examined regular use of low dose (<100 mg) ASA, the reduced risk was even stronger (OR 0.66, 95% CI 0.53 to 0.83). Stratification according to histologic subtypes found risk reductions for serous, endometrioid, and mucinous "ovarian" cancers. However, the results were only statistically significant for invasive serous cancers (OR 0.89, 95% CI 0.80 to 0.99). Regular non-ASA, non-steroidal anti-inflammatory drug use was associated with a reduced, albeit not statistically significant, risk of "ovarian" cancer (OR 0.90, 95% CI 0.77 to 1.05). This review did not show a risk reduction with regular use of acetaminophen.[75]

Contrary to these findings, a Danish population-based study of 3471 cases and 50 576 controls found that the regular use of acetaminophen was associated with a reduced OR of "ovarian" cancer (OR 0.82, 95% CI 0.74 to

0.92; $P < 0.001$).[76] The reduction was even greater with "high intensity use" of acetaminophen (OR 0.45, 95% CI 0.24 to 0.86; $P = 0.02$). The use of other non-ASA, non-steroidal anti-inflammatory drugs was not associated with a reduced risk of "ovarian" cancer in this study.

Population-based screening

Numerous studies have examined the use of population-based screening for early detection of "ovarian" cancer. Three recent large, prospective, randomized trials have not demonstrated a significant difference between the control and screened groups in the number of women who have died from "ovarian" cancer but have demonstrated an increase in interventions in screened women, with resulting morbidity. These include the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial in the United States,[77] the United Kingdom Trial of Ovarian Cancer Screening,[78] and the Shizuoka Cohort Study of Ovarian Cancer Screening trial.[79]

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial randomly assigned 68 616 women aged 55 to 74 to screening with a serum CA 125 assay and pelvic ultrasound or no screening.[77] After a median follow-up of 12 years, there had been 118 deaths in the screened cohort and 100 deaths in the controls. The mortality rate ratio was 1.18 (95% CI 0.91 to 1.54).[77]

The United Kingdom Trial of Ovarian Cancer Screening randomly assigned 202 638 women from the general population to a treatment protocol.[78] Randomization took place between 2001 and 2005. Women were randomly assigned to have either no screening, annual screening with transvaginal ultrasound, or annual serum CA 125 plus algorithm-based transvaginal ultrasound (multimodal strategy). At a median follow-up of 11.1 years, 154 women (0.30%) in the transvaginal ultrasound screening group, 148 (0.29%) in the multimodal screening group, and 347 (0.34%) in the no screening group had died of "ovarian" cancer. There was a small trend towards better survival in the later years of the study; however, this may reflect lead-time bias. A longer duration of follow-up is required to determine the true effect on mortality and cost-effectiveness of "ovarian" cancer screening.[78]

The Shizuoka Cohort Study randomly assigned 82 487 low-risk postmenopausal women to either no screening or screening with annual ultrasound and serum CA 125 assay.[79] No significant difference was found in the number of women who developed "ovarian" cancer in the screened and control groups (27 and 32 women, respectively).

Infertility and use of ovulation stimulating drugs

Linking the use of ovulation stimulating drugs with the risk of "ovarian" cancers is complicated because infertility itself is a risk factor for the development of "ovarian" cancer.[80] Studies examining this relationship must address potential confounders that include parity, type of fertility treatment, and number of fertility treatment cycles. To date, information regarding the relationship between fertility treatment and "ovarian" cancer has come primarily from retrospective, cohort and case control studies. Whereas older studies suggested a relationship between fertility treatment and cancer, newer studies that account for potential confounders have not demonstrated this relationship.[81]

Trabert et al.[81] reviewed a retrospective cohort of 9825 women experiencing infertility to look for an association between clomiphene use or gonadotropin use and "ovarian" cancer. For those women who had used clomiphene, the RR of "ovarian cancer" was 1.34 (95% CI 0.86 to 2.07). The RR did not increase with increasing exposure to clomiphene. The RR of "ovarian" cancer for women who had used gonadotropins was 1.0 (95% CI 0.48 to 2.08). The only subgroup in this study that had a significant risk of "ovarian" cancer was the group that used clomiphene and remained nulligravida (RR 3.63, 95% CI 1.36 to 9.72).

The Mayo Clinic Ovarian Cancer Study compared 1028 women with "ovarian" tumours with 872 control patients. The OR of developing "ovarian" tumours for infertile women who used fertility drugs compared with infertile women who did not was 0.64 (95% CI 0.37 to 1.11).[82] A retrospective cohort study from Israel specifically examined IVF and risk of cancer development. In this cohort of 87 403 women the HR of "ovarian" cancer associated with the use of IVF was 1.58 (95% CI 0.75 to 3.92). This HR increased slightly in the category of women receiving 4 or more IVF cycles but remained statistically insignificant (HR 1.78, 95% CI 0.76 to 4.13).[83] A recent meta-analysis of 9 studies analyzed data from 109 969 women who underwent IVF. Seventy-six women in this cohort developed "ovarian" cancer. In those studies using the general population as a reference group, the RR of "ovarian" cancer was found to be 1.5 (95% CI 1.17 to 1.92). In those studies using infertile women who did not undergo IVF as the reference group, the RR risk of "ovarian" cancer was 1.26 (95% CI 0.62 to 2.55).[84]

In summary, infertility treatments do not increase the risk of "ovarian" cancer. However, women who use fertility treatments and remain nulligravida do have an increased risk of "ovarian" cancer.

Endometriosis and the risk of endometrioid and clear cell ovarian cancers

If endometriosis does indeed play a role in the development of clear cell and endometrioid "ovarian" cancers, it would follow that treating endometriosis should lower the risk of these cancers.[85] A case control study conducted in Sweden compared 220 treated cases with 416 matched controls.[86] All the women reviewed in this study had been identified as having endometriosis. Women who had undergone unilateral oophorectomy and/or aggressive surgical resection of endometriosis were found to have a significantly reduced risk of "ovarian" cancer (adjusted OR 0.30, 95% CI 0.12 to 0.74).[86]

Summary Statements

8. Oral contraceptive pill use effectively reduces the lifetime risk of developing an "ovarian" cancer by 50% when taken for more than 10 years (High).
9. Tubal ligation reduces the risk of endometrioid cancer by 52% and clear cell cancer by 48%, presumably by blocking retrograde menstruation and preventing endometriotic deposits within the pelvis. However, tubal ligation reduces the risk of developing high-grade serous cancers by only 19%, supporting the theory that these cancers arise within the distal end of the remaining fallopian tube (Moderate).
10. The strategy with greatest potential for risk reduction is bilateral salpingo-oophorectomy, which reduced the mortality rate from "ovarian" cancer in the Nurses' Health Study by 94%; however, the overall risk of death from any cause following bilateral salpingo-oophorectomy increased by 12%, reflecting the protective effect of estrogen in preventing cardiovascular disease before age 50 (High).
11. The effect of diet and obesity on "ovarian" cancer risk is currently unclear and requires further research (Low).
12. The role of metformin in the primary prevention of "ovarian" cancer needs further research for clarification (Low).
13. There is insufficient evidence to link the use of talc-containing products with "ovarian" cancer (Moderate).
14. Acetylsalicylic acid has been shown to reduce the risk of "ovarian" cancer, but the effect of non-acetylsalicylic acid non-steroidal anti-inflammatory drugs and acetaminophen is unclear (Moderate).
15. There has been no effective screening protocol to date that can decrease mortality from "ovarian" cancer in the general population (Moderate).
16. There is no established link between the use of "ovulation stimulating drugs" and "ovarian" cancer (Moderate).
17. Treating endometriosis may reduce the risk of "ovarian" cancer (Low).

Recommendations

1. The use of an oral contraceptive pill reduces the risk of users developing high-grade serous cancers and should be discussed when counselling women on contraceptive use (Strong, High).
2. When considering permanent contraception, tubal ligation is shown to have the additional benefit of reducing the risk of developing high-grade serous cancers. However, the fact that the complete removal of the fallopian tube may provide additional benefit should be discussed (Strong, High).
3. Removal of the ovaries in premenopausal women may increase the risk of cardiovascular disease and is not recommended without clinical indication (Strong, High).
4. Population-based screening should not be encouraged as a method of "ovarian" cancer risk reduction (Strong, High).

Current Literature on the Effects and Safety of Opportunistic Salpingectomy

There is mounting evidence demonstrating the safety of opportunistic salpingectomy. A salpingectomy can often be safely done at the time of vaginal hysterectomy, with a recent study showing an overall completion rate of 88%.[87] However, no additional surgical procedures should be performed to access the fallopian tubes. A single paper concerning salpingectomy at CS of 16 cases with salpingectomy, compared with 64 cases of BTL, was published September 2016. The average surgical time was slightly statistically longer in the BTL and salpingectomy cohorts by an average of 12 minutes. One patient had an estimated blood loss over 50 mL; this patient was in the BTL group. Four complications were noted in the BTL cohort, but none was evident in the salpingectomy group. The procedure appears to be safe at the time of CS; however, there has been no long-term follow-up and the cases are few.[88] When performing a salpingectomy, instead of a tubal ligation, an additional port is usually required. The additional port may need to be a larger diameter to facilitate removal of the fallopian tubes.

Three retrospective cohort studies found no difference in complication rates, length of hospital stay, or overall

recovery times for patients undergoing an opportunistic salpingectomy at the time of hysterectomy.[89–91] Morelli et al.[90] further evaluated their cohort postoperatively for ovarian reserve using hormone testing and antral follicle count at 3 months after surgery and found no differences between women who had their fallopian tubes removed and women who did not. There are no published findings concerning the long-term effects of opportunistic salpingectomy on ovarian function. Moreover, one study found that women who retained their fallopian tubes had a significantly increased rate of benign adnexal pathologies requiring surgical intervention (12.6%) compared with those who underwent salpingectomy (4.2%).[91]

A Danish population-based study of 170 000 women compared the rates of surgical re-intervention for tubal pathology following a hysterectomy with and without retention of fallopian tubes (n = 6456).[92] The authors found that the risk of repeat surgery among women with retained fallopian tubes was at least doubled (OR 2.13, 95% CI 1.88 to 2.42), and they recommended that fallopian tubes should be removed at hysterectomy. However, this population-based study was not designed to evaluate whether the incidence of HGSC was reduced with the inclusion of salpingectomies. None of the aforementioned retrospective studies had a sample size large enough or a follow-up period long enough to evaluate whether a change in surgical practice to routine removal of the fallopian tubes will reduce the HGSC rate in the general population. A meta-analysis demonstrated that 3509 women who underwent bilateral salpingectomy had a reduction in "ovarian" cancer compared with 5 655 702 control patients (OR 0.51, 95% CI 0.35 to 0.75).[93] This meta-analysis included all types of "ovarian" cancer and did not include further analysis based on pathologic subtype. A population-based study from Sweden evaluated "ovarian" cancer risk reductions associated with bilateral salpingectomy, BTL, hysterectomy, and hysterectomy with bilateral salpingo-oophorectomy (n = 251 465) compared with a control population (n = 5 449 119).[94] Statistically significant risk reductions were observed among women with BTL (HR 0.72, 95% CI 0.64 to 0.81); hysterectomy (HR 0.79, 95% CI 0.70 to 0.88); and hysterectomy with bilateral salpingo-ophorectomy (HR 0.06, 95% CI 0.03 to 0.12). Bilateral salpingectomy reduced the risk by 65% (HR 0.35, 95% CI 0.17 to 0.73), a much greater reduction than that associated with BTL, reflecting the effect of removal of the fimbriated end of the fallopian tube.

To evaluate a change in the HGSC rate, a prospective population-based study is required. This is ongoing in British Columbia in a regional initiative begun in 2010 and aimed at general gynaecologists within that province.[95] By encouraging general gynaecologists to consider removal of fallopian tubes at the time of every hysterectomy and sterilization procedure and referral of all patients with HGSC for hereditary cancer counselling and genetic testing, they project a 40% reduction in the rate of HGSC in British Columbia over the next 20 years. The first analysis of a retrospective review of 43 931 women in British Columbia who underwent hysterectomy between 2008 and 2011 found an increase in the uptake of opportunistic salpingectomy at the time of hysterectomy (from 5% to 35%) and sterilization (from 0.4% to 33%), with minimal additional operating time and no difference in the rates of complications or hospital readmission. Maturation of these prospective study results will take at least 15 years.[95]

The multiple studies showing that this additional procedure can be performed safely and can prevent further operative interventions for benign adnexal pathology provide strong reasons for care providers in the remainder of Canada to recommend opportunistic salpingectomy.

Summary Statements

18. Performing opportunistic salpingectomy at the time of hysterectomy for benign gynaecologic disorders does not increase complication rates, length of hospital stay, or overall recovery time but does lead to a minor increase in surgical time (Moderate).
19. Retaining the fallopian tubes at the time of hysterectomy increases the risk of subsequent reoperation for tubal pathology (Moderate).
20. Population-based studies are required to evaluate whether opportunistic salpingectomy can reduce the incidence of high-grade serous cancers (Moderate).

Recommendations

5. In considering hysterectomy with the ovaries remaining in situ, the fact that the removal of easily accessible fallopian tubes may reduce the risk of developing high-grade serous cancers without additional procedural risk, and is recommended, should be discussed (Strong, Moderate).
6. Prospective population-based surgical databases should be kept to monitor the effect of opportunistic salpingectomy on overall morbidity and mortality and especially the rates of high-grade serous cancers (Strong, Moderate).

CONCLUSION

For women who develop HGSC, the morbidity arising from treatment and the overall mortality from the disease are very high, and there are few prospects for an effective screening process to reduce the risk of developing this cancer. There is a growing body of evidence indicating that HGSC originates within the fallopian tube. Opportunistic salpingectomy can be performed safely at the time of hysterectomy or permanent sterilization, can prevent further operative interventions for benign adnexal pathology, and can potentially reduce the risk of developing HGSC. In premenopausal women, salpingectomy does not appear to affect ovarian function, but this possibility should be discussed before surgery. If the fallopian tubes are inaccessible at the time of surgery, additional surgical steps should not be performed to access them.

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