The Fallopian Tube as the Origin of High Grade Serous Ovarian Cancer: Review of a Paradigm Shift

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Abstract

Research published over the past 10 years has suggested that most "ovarian cancer," and specifically the high-grade serous carcinoma (HGSC) subtype of ovarian cancer, actually originates in the fallopian tube. In this review, we examine the evidence supporting the tubal origin hypothesis for HGSC, and discuss the clinical implications of our improved understanding of the pathogenesis of ovarian cancer. We searched Medline R and Medline in-process and non-indexed citations from inception to December 15, 2012, to identify all English or French language articles discussing the origins of HGSC. Articles and findings were summarized descriptively. A step-wise transformation from normal epithelium to a lesion with the ability to invade and metastasize has been demonstrated within the fallopian tube. Intraepithelial or early invasive carcinoma of the fallopian tube is frequently identified in BRCA mutation carriers who undergo prophylactic risk-reducing salpingo-oophorectomy. In both BRCA mutation carriers and women from the general population, pre-invasive changes within the fimbriated end of the fallopian tube appear in association with early HGSC. Molecular and genetic studies, as well as in vitro and animal models, have also supported a tubal origin for HGSC. Whether the removal of fallopian tubes (salpingectomy) at the time of pelvic surgery for other reasons will lead to reductions in mortality from ovarian cancer is currently unknown, but it is an important area for future clinical research.

Résumé

Les recherches publiées au cours des 10 dernières années ont laissé entendre que la plupart des « cancers de l'ovaire » (et plus particulièrement le sous-type « carcinome séreux de haut grade histologique » [CSHG] du cancer de l'ovaire) trouvent en fait leur origine dans la trompe de Fallope. Dans le cadre de cette analyse, nous examinons les données soutenant l'hypothèse de l'origine tubaire du CSHG et nous discutons des implications cliniques de notre compréhension améliorée de la pathogenèse du cancer de l'ovaire. Nous avons mené des recherches dans Medline R et dans les citations en traitement et non répertoriées de Medline en vue d'en tirer tous les articles publiés en anglais ou en français discutant des origines du CSHG, et ce, du début de notre étude jusqu'au 15 décembre 2012. Les articles et les constatations ont été résumés de façon descriptive. Une transformation progressive de l'épithélium normal en lésion ayant la capacité d'envahir les tissus voisins et de produire des métastases a été démontrée au sein de la trompe de Fallope. La présence d'un carcinome intraépithélial ou invasif précoce de la trompe de Fallope est fréquemment identifiée chez les porteuses de la mutation BRCA qui subissent une salpingo-ovariectomie prophylactique d'atténuation du risque. Tant chez les porteuses de la mutation BRCA que chez les femmes de la population générale, des modifications préinvasives affectant la frange ovarienne se manifestent en association avec l'apparition d'un CSHG précoce. Des études moléculaires et génétiques (ainsi que des études *in vitro* et menées sur des modèles animaux) ont également soutenu l'hypothèse de l'origine tubaire du CSHG. Bien que nous ne disposions toujours pas d'une réponse à la question de savoir si le retrait des trompes de Fallope (salpingectomie) au moment d'une chirurgie pelvienne effectuée pour d'autres raisons mène à une baisse du taux de mortalité attribuable au cancer de l'ovaire, elle demeure néanmoins un domaine d'intérêt important pour les futures recherches cliniques.

Key Words: Ovarian cancer, high-grade serous carcinoma, tubal origin hypothesis, serous tubal intraepithelial carcinoma, salpingectomy, HGSC

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INTRODUCTION

Ovarian cancer is the fifth most common cause of death from cancer among women in Canada, and is the most lethal gynaecologic malignancy.[1] The median age of women with ovarian cancer is 60 years, and approximately one in 70 women will develop ovarian cancer in her lifetime.[2] Treatment includes a combination of cytotoxic chemotherapy and surgery that aims to excise all visible disease. Although appropriate treatment can lead to a lengthy progression-free interval in many, it is rarely curative for women with advanced-stage disease. The median overall length of survival after diagnosis has improved, but long-term cure rates for women with ovarian cancer have not changed over the past 20 years.[3] This has driven the search for better treatment strategies and earlier detection. Improving survival for women with ovarian cancer requires a better understanding of the pathogenesis and origin of this disease.[4]

Epithelial ovarian cancer is a heterogeneous disease made up of several histologic subtypes which have different genetic profiles and clinical behaviours.[5,6] The most common subtype, high-grade serous carcinoma, is responsible for the majority of deaths from ovarian cancer, and is also the subtype seen in cases of primary peritoneal and fallopian tube carcinoma (primary peritoneal carcinoma is considered to be included in the term "ovarian cancer" for the purposes of this review).[7] Sixty to eighty percent of ovarian epithelial malignancies have HGSC histology.[2,8,9] HGSC typically presents at an advanced stage, with > 80% diagnosed at International Federation of Gynaecology and Obstetrics stages III to IV.[10] To date, no screening regimens for HGSC have been proven effective.[11,12] In the past, the precise pathogenesis of HGSC was poorly defined, evading physicians and scientists for decades.[9] Emerging evidence suggests that most HGSC may in fact arise from the secretory epithelium of the distal fallopian tube. This paradigm shift in our understanding of the pathogenesis of ovarian cancer may open the door to novel preventive and therapeutic strategies.

Salpingectomy at the time of other gynaecologic surgery, such as hysterectomy with ovarian conservation or as a method of permanent contraception, has been proposed as a strategy to prevent HGSC by gynecologic oncologists with the Ovarian Cancer Research Program at the Vancouver General Hospital (VGH) and BC Cancer Agency.[13] This issue has been widely publicized in the Canadian media in recent years,[14] but little peer-reviewed literature has been published in Canadian medical journals.[15] In our previous survey of Canadian obstetrician-gynaecologists,[15] many physicians wanted additional information about the fallopian tube hypothesis for the pathogenesis of HGSC before they would commit to a change in surgical practice to perform salpingectomy at the time of other gynaecologic surgery. Responding to this need, we review here the evidence supporting the hypothesis that HGSC originates from the fallopian tube, rather than the ovary, in a large proportion of cases.

ABBREVIATIONS

HGSC	high-grade serous carcinoma
RRSO	risk-reducing salpingo-oophorectomy
SEE-FIM	Sectioning and Extensively Examining the FIMbria
STIC	serous tubal intraepithelial carcinoma

METHODS

We searched Medline R and Medline in-process and non-indexed citations from inception to December 15, 2012, to identify all English or French-language publications of salpingectomy for ovarian cancer prevention and the fallopian tube hypothesis of HGSC. The search strategy incorporated appropriate, controlled vocabulary and key word searches including various terms for salpingectomy and combining these with terms for ovarian cancer or HGSC, and prevention. Terms for ovarian cancer were also combined with terms such as tubal intraepithelial carcinoma. The search strategy is specified in the Table. In addition, the PubMed related articles feature was used to ensure all relevant articles were identified. Articles were separated into relevant categories and a narrative synthesis of the literature prepared. Meta-analysis was not appropriate for the synthesis of results, since articles generally did not examine patient outcomes.

RESULTS

Dubeau first suggested the possibility that "ovarian cancers" may originate from structures of the Mullerian system, including the fallopian tube, in 1999.[16] This was based on the observations that serous ovarian cancers have the appearance of fallopian tube epithelium and that no such (serous) epithelium is observed in normal ovaries, as well as the fact that no precancerous lesions have been identified in the ovary. Serous carcinomas of the ovary, fallopian tube, and peritoneum have an identical histologic appearance and clinical behaviour, and the designation of origin has historically been based on the location of the bulk of tumour, despite the fact that most patients have disseminated disease.[17,18]

Carcinoma of the fallopian tube was first identified in BRCA2 mutation carriers in 1997[19] and in BRCA1 carriers in 2000,[20] introducing the concept that cancers of the fallopian tube are part of the spectrum of disease associated with BRCA mutations. Risk-reducing salpingo-oophorectomy has been recommended for BRCA mutation carriers to reduce the risk of ovarian cancer.[21] However, after the link between BRCA and fallopian tube cancers was published, pathologists began evaluating the fallopian tubes from these RRSO specimens more carefully. Several large series of RRSO specimens from BRCA carriers found a high frequency of occult cancers in the fallopian tubes (ranging from 4.4% to 17%), especially when the entire tube was serially sectioned.[22,23] Tubal involvement (HGSC identified within the fallopian tube) was present in 42% to 100% of patients diagnosed with HGSCs in various series of BRCA patients undergoing RRSO.[24–26]

Aside from macroscopic fallopian tube carcinomas, studies of RRSO specimens from BRCA mutation carriers also identified an early form of serous carcinoma in situ, still confined to the mucosal surface of the fimbria.[27–29] Variously termed "tubal intraepithelial carcinoma," "serous tubal intraepithelial carcinoma," or "serous intraepithelial carcinoma," this entity has the histologic appearance of HGSC without invasion of the basement membrane, and also positive immunostaining for p53 and Ki-67, similar to invasive HGSC.[27] This entity appears to be able to spread through the peritoneal cavity even before local invasion within the tube.[26,27] When the fallopian tubes were sectioned using the SEE-FIM protocol[24] to examine the fimbriated end carefully, all occult cancers identified in BRCA carriers' RRSO specimens also had associated STIC in the fimbria in one series.[27]

A precursor to STIC has also been identified, and has been termed the "p53 signature."[24] A p53 signature is a section of exclusively secretory, benign-appearing, tubal epithelium that has developed a p53 mutation, but does not have marked histologic cellular atypia and has a normal proliferation index (normal Ki-67).[24] This lesion appears in association with STIC[30] and HGSC, but also in the fimbriated ends of normal fallopian tubes from both BRCA1/2 mutation carriers and the general population.[30–32] These p53 signatures are not associated with disseminated disease in the absence of STIC, suggesting they are only the first step along the HGSC continuum.[17,30]

A step-wise acquisition of mutations is the biologic rationale for the tubal origin hypothesis of pelvic serous carcinoma: first appearing as p53 signatures, then as STIC, and finally, as HGSC.[24] A large pathological study examining fallopian tubes in RRSO specimens from women undergoing

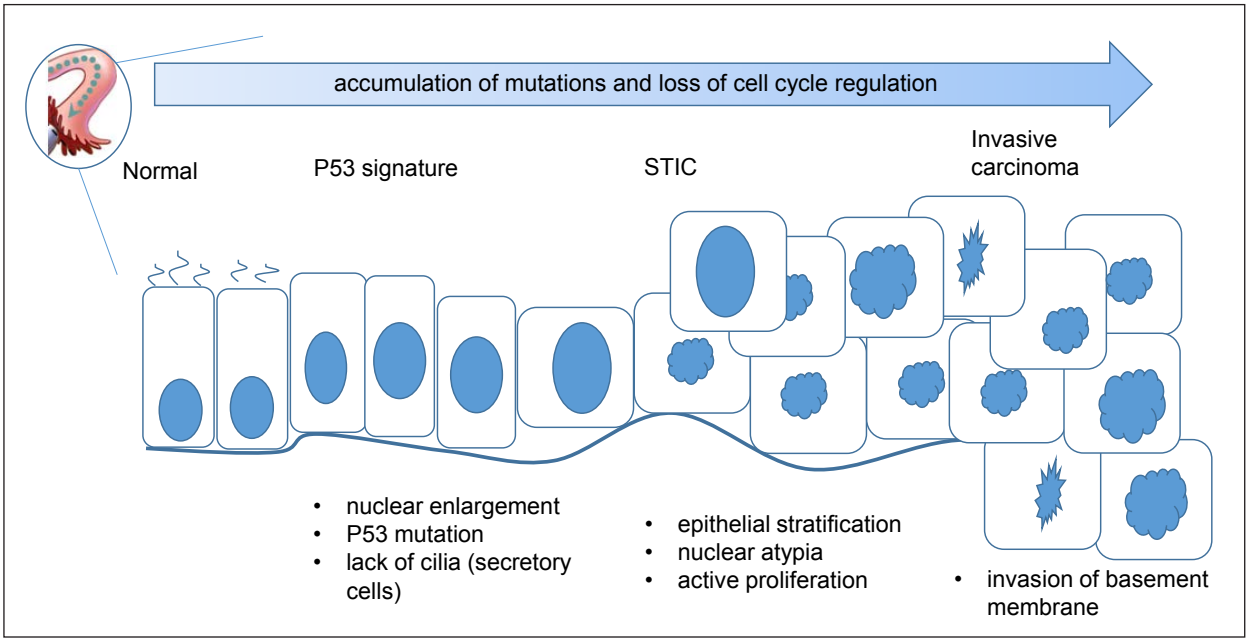
Search strategy: tubal origins of ovarian high grade serous carcinoma and salpingectomy to prevent ovarian cancer

Databases: 1. MEDLINE R 1946 to November 2012 week 3
2. MEDLINE in-process and non-indexed citations
Search Date: December 15, 2012.
Limits: none

Syntax guide	
/	At the end of a phrase, searches the phrase as a subject heading
.mp	Keyword search
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals of varying endings
Adj	Adjacency modifier
?	Truncation symbol for one or no characters only

#	Search terms	Results
1	exp Salpingectomy/	216
2	salpingectomy.mp	1241
3	1 OR 2	1241
4	exp Pregnancy, Ectopic/	12 641
5	ectopic pregnancy.mp	6826
6	4 OR 5	14 320
7	3 NOT 6	602
8	Ovarian Neoplasms/	58 211
9	(ovarian adj3 cancer).mp	31 728
10	(ovarian adj3 carcinoma).mp	11 009
11	(cancer adj3 ovary).mp	802
12	(carcinoma adj3 ovary)	1353
13	high grade serous cancer.mp	8
14	high grade serous carcinoma.mp	101
15	HGSC.mp	32
16	OR/8–15	67 215
17	7 AND 16	98
18	exp Secondary Prevention/ or exp Primary Prevention/	107 611
19	prevent*.mp	898 632
20	18 OR 19	980 659
21	17 AND 20	13
22	tubal intraepithelial carcinoma.mp	41
23	serous tubal intraepithelial carcinoma.mp	22
24	TIC.mp	3987
25	STIC.mp	207
26	OR/22–25	4201
27	16 AND 26	44
28	21 OR 27	57

The rate of accumulation of mutations may be influenced by retrograde menstruation, with passage of menstrual blood containing inflammatory cytokines along the tubal epithelium, by damage and repair caused by ovulation, by the presence of infectious agents or irritants, or by loss or absence of DNA damage repair genes such as BRCA-1 or 2.



surgery for HGSC and from women undergoing benign gynaecologic surgery observed areas of transition between p53 signatures, STIC, and HGSC.[33] This further supports the concept of a spectrum of neoplastic changes leading from normal fallopian tube epithelium to HGSC. This progression is illustrated in the Figure. A similar pattern of precursors for HGSC has not been observed in the ovary.[32]

The model outlined above for the transformation of normal fallopian tube epithelium to HGSC applies to both BRCA mutation carriers and to the general population. In a series of macroscopic fallopian tube cancers, both BRCA-associated and sporadic cases appeared to involve the fimbriated end of the tube.[34] This supports the proposal that there is a common at-risk area within the fallopian tubes for both BRCA positive and negative women. In a screening trial using assays of serum CA-125 to try to detect early ovarian cancers in the general population, the ratio of ovarian to fallopian tube cancers was 6:1; this was 25 times higher than expected, suggesting that the fallopian tube may be involved early in the disease process of HGSC.[35] In a large series of ovarian, fallopian tube, and primary peritoneal HGSC in consecutive women in which the SEE-FIM protocol was employed, tubal mucosal involvement with STIC or invasive carcinoma was present in 75% of cases.[36] In this series, 93% of STIC lesions were located in the tubal fimbria.[36] In a similar unselected consecutive series of ovarian, fallopian tube, and primary peritoneal carcinomas, STIC was found only in association with HGSC (not with other histologic subtypes) and was observed in 60% of HGSC.[37]

Molecular and genetic evidence has also been published, strengthening the link between tubal epithelium, STIC, and HGSC in both BRCA1/2 mutation carriers and the general population. Sequencing of the p53 gene was undertaken in five cases of STIC, in conjunction with HGSC with predominantly ovarian involvement, from unselected women. Identical mutations were found in each pair of STIC and HGSC from the ovary, suggesting a genetic link between the two lesions in these five individuals.[36] This experiment has been repeated in a series of 29 patients, with a 93% rate of concordance between STIC and HGSC involving the ovary.[38]

An in vitro experiment using an immortalized normal fallopian tube epithelium cell line found that these cells could produce an entity histologically and clinically identical to HGSC in mice after introduction of genetic alterations, including, but not limited to, mutation of p53.[4] This study essentially demonstrated the process of neoplastic transformation of tubal epithelial cells into HGSC in vitro.[4]

Studies in hens ovulating daily noted high rates of serous carcinoma[39]; all cases of serous carcinoma were associated with tubal pre-neoplastic and neoplastic lesions, regardless

of the distribution of serous cancer at diagnosis.[40] This is consistent with the long-held belief that ovarian carcinogenesis is promoted by incessant ovulation[41,42] in addition to having a tubal origin. It has been proposed that incessant exposure of the (secretory) epithelial cells in the distal fallopian tube to locally elevated levels of inflammatory cytokines and reactive oxygen species after ovulation each month could contribute to the development of precursor lesions and eventual malignant transformation of these cells. This process would be mediated through the accumulation of DNA damage, mutation of p53 and accumulation of additional genetic aberrations, and is supported by expression of the DNA damage marker γ-H2AX in p53 signatures and STIC lesions in humans[43] and in tubal epithelial cells in superovulated mice.[44] Epidemiologic studies have also reported inverse correlations between the presence of a tubal precursor and both oral contraceptive use[45] and parity,[46] factors known to alter the number of lifetime ovulations. Finally, global gene expression profiles of non-malignant fallopian tube epithelium cells from BRCA mutation carriers obtained during the luteal phase closely resemble those of tubal and ovarian HGSC[47]; a subset of these changes has been found to be affected by BRCA1 status.[48]

DISCUSSION

The current approach to the diagnosis and management of ovarian cancer has led to marginal improvements in overall survival in recent decades.[49] This is likely because the majority of ovarian cancers are HGSC, and these are generally diagnosed at an advanced stage; there is currently no effective screening test that can lead to prevention or early diagnosis of HGSC.[11,12] In addition, while our standard approach is to treat all ovarian cancers in the same way, ovarian cancer is not a single disease. It requires a histologic subtype-specific approach. Because most HGSC likely originates from the fallopian tube, low-grade serous cancers originate from the ovarian surface epithelium, and most endometrioid and clear cell histologic subtypes originate from endometriosis (with differences in genomic profiles and clinical course[50]), recognizing differences in site of origin is essential for future clinical trials and for developing strategies for prevention and treatment.[17,51,52]

HGSCs account for 60% to 80% of all ovarian cancers, and frequently present in an advanced stage.[2] The origin of HGSC is critically important in the development of effective treatment and prevention strategies, since it is this histologic subtype that accounts for most mortality from ovarian cancer. Unfortunately, efforts to reduce ovarian cancer-related mortality by improvements in systemic therapy have been disappointing. In oncology drug development, 60% of phase 2 clinical trials fail to demonstrate success in subsequent phase 3 investigations.[53] The cost of developing new antineoplastic agents is unsustainably high, with attrition rates in drug development of over 90%.[10] The need for a clearer understanding of the biology of all histologic subtypes of ovarian cancer is undisputed and is the beginning of a paradigm shift in the way we treat "ovarian cancer."

HGSC represents a distinct clinical challenge, given its late clinical presentation and aggressive nature. HGSC is associated with mutations in the DNA damage-repair genes BRCA1 and BRCA2.[54,55] RRSO before the age of 40 significantly reduces the risk of ovarian cancer in women who are BRCA mutation carriers, and this procedure is recommended for these women who are at very high lifetime risk of HGSC.[56–58] However, removal of the ovaries in premenopausal women has been associated with an increased risk of cardiovascular disease, Parkinsonism, cognitive impairment, depression and anxiety, and, most importantly, all-cause mortality.[59–63] Many BRCA mutation carriers are unwilling to undergo RRSO because of these risks, and because of the decrease in quality of life associated with premature menopause.[64] So, the pertinent question is "If most HGSC originates in the fallopian tubes, is salpingectomy alone enough to prevent ovarian cancer in BRCA mutation carriers?"

Performing salpingectomy alone has the advantages of maintaining ovarian hormonal function and preserving fertility (with the use of assisted reproductive technologies).[65,66] However, there is not yet any clinical evidence that salpingectomy alone is an effective risk-reducing strategy for women with BRCA mutations. RRSO also reduces the risk of breast cancer in premenopausal BRCA carriers by up to 50%[67]; this is a benefit not expected from salpingectomy. Salpingectomy, therefore, cannot be recommended at present as an alternative to RRSO in these high-risk patients. However, there may be a role for salpingectomy as an interim procedure for selected patients who are unwilling to undergo RRSO. Kwon et al. developed a Markov Monte Carlo simulation model to estimate the costs and benefits of three risk-reducing strategies in BRCA mutation carriers who have not yet had breast or ovarian cancer: (1) bilateral salpingo-oophorectomy at age 40 years, (2) bilateral salpingectomy at age 40 years, and (3) bilateral salpingectomy at age 40 years followed by bilateral oophorectomy at age 50 years.[68] They found that bilateral salpingo-oophorectomy was associated with the lowest cost and highest life expectancy compared with the other two strategies. However, when quality-of-

life measures were included, salpingectomy followed by delayed oophorectomy yielded the highest quality-adjusted life expectancy. This strategy may prove to be the most acceptable in this young population, and it deserves further prospective study.

Could we also use this information to prevent ovarian cancer in women in the general population who are at average risk of ovarian cancer? Thousands of hysterectomies, tubal ligations, and other pelvic surgical procedures are performed in Canadian women each year. Salpingectomy at the time of other pelvic surgery has been much publicized as a potential strategy to reduce the risk of ovarian cancer in the general population.[13,14] There is currently no clinical evidence to show that salpingectomy reduces the risk of ovarian cancer, and, given the age of women in the general population who are undergoing salpingectomy, it will be many years before we anticipate seeing an impact on ovarian cancer incidence or distribution of histologic subtypes of ovarian cancer. Theoretically, salpingectomy may reduce the incidence of both HGSC (because of the site of origin of most cases in the fallopian tube) and endometrioid and clear cell ovarian cancers (because of removal of the conduit for retrograde passage of endometrial tissue).

Prospective clinical evaluation of salpingectomy outcomes is an important area for future investigation. Salpingectomy is expected to add very little to no extra OR time, cost, or morbidity for most pelvic procedures. Morelli et al. performed a retrospective study comparing women undergoing laparoscopic hysterectomy with those having laparoscopic hysterectomy with salpingectomy. There was no increase in surgical complications, operative time, or blood loss, and no change in any measure of hormonal function associated with the addition of salpingectomy.[65] Similarly, Sezik et al. performed a randomized controlled trial of abdominal hysterectomy with and without salpingectomy and found no change in ovarian hormonal function after salpingectomy.[66]

Although the evidence suggests that most ovarian cancer begins in the fallopian tubes, there is currently a lack of evidence of clinical benefit from performing salpingectomy; therefore, if considering whether or not a patient should undergo salpingectomy, clinicians must discuss the risks and benefits with patients on a case-by-case basis.[15] A 2011 statement from the Society of Gynecologic Oncology of Canada recommended this approach until more clinical evidence is available.[69]

Despite the accumulating evidence supporting a tubal origin of HGSC, clinical trials investigating the benefits of salpingectomy are lacking. To our knowledge, no studies have yet been published evaluating salpingectomy without oophorectomy as a method for preventing ovarian cancer in women with or without BRCA mutations. There is a need for rigorous evaluation of salpingectomy for women at high risk who prefer ovarian conservation, and for women in the general population undergoing gynaecologic surgery for other reasons. Collaborative research efforts should be supported with public funds, given the potential to create a significant public health impact from earlier diagnosis or prevention of this aggressive disease.

CONCLUSION

Given the plausible concept of a tubal origin for the majority of HGSC, we must now translate our understanding of the pathogenesis of HGSC into more effective prevention and treatment for patients with this disease. This is an exciting area of medicine, with the prospect of translational research leading to tangible clinical benefits for patients. All clinicians providing care for women should understand current concepts in the pathogenesis of this disease, which is such an important contributor to early cancer-related mortality in Canadian women.

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REFERENCES

1. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian cancer statistics 2012. Toronto, ON: Canadian Cancer Society; 2012. Available at: http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2012—English.pdf. Accessed October 25, 2013.
2. Cannistra SA. Cancer of the ovary. N Engl J Med 2004;351(24):2519–29.
3. Engel J, Eckel R, Schubert-Fritschle G, Kerr J, Kuhn W, Diebold J, et al. Moderate progress for ovarian cancer in the last 20 years: prolongation of survival, but no improvement in the cure rate. Eur J Cancer 2002;38(18):2435–45.
4. Karst AM, Levanon K, Drapkin R. Modeling high-grade serous ovarian carcinogenesis from the fallopian tube. Proc Natl Acad Sci U S A 2011;108(18):7547–52.
5. Ioka A, Tsukuma H, Ajiki W, Oshima A. Ovarian cancer incidence and survival by histologic type in Osaka, Japan. Cancer Sci 2003;94(3):292–6.
6. Kurman RJ, Shih I-M. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer—shifting the paradigm. Hum Pathol 2011;42(7):918–31.
7. Agoff SN, Mendelin JE, Grieco VS, Garcia RL. Unexpected gynecologic neoplasms in patients with proven or suspected BRCA-1 or -2 mutations: implications for gross examination, cytology, and clinical follow-up. Am J Surg Pathol 2002;26:171–8.
8. Seidman JD, Horkayne-Szakaly I, Haiba M, Boice CR, Kurman RJ, Ronnett BM. The histologic type and stage distribution of ovarian carcinomas of surface epithelial origin. Int J Gynecol Pathol 2004;23(1):41–4.

9. Levanon K, Crum C, Drapkin R. New insights into the pathogenesis of serous ovarian cancer and its clinical impact. J Clin Oncol 2008;26(32):5284–93.
10. Vang R, Shih I-M, Kurman RJ. Ovarian low-grade and high-grade serous carcinoma. Adv Anat Pathol 2009;16(5):267–82.
11. Reade CJ, Riva JJ, Busse JW, Goldsmith CH, Elit L. Risks and benefits of screening asymptomatic women for ovarian cancer: a systematic review and meta-analysis. Gynecol Oncol 2013;130(3):674–81.
12. Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA 2011;305(22):2295–303.
13. BC Cancer Agency. Ovarian cancer researchers request practice changes to protect against ovarian cancer (deaths could be reduced 50 percent over 20 years). News Release Archive 1997–2010; 2010 News [News Release]. Available at: http://www.bccancer.bc.ca/ABCCA/NewsCentre/NewsArchive/2010-News-Releases/Ovarian+cancer+researchers+request+practice+changes+to+protect+against+ovarian+cancer.htm. Accessed August 3, 2011.
14. CBC. Fallopian tube removal cuts ovarian cancer risk. CBC News: Health 2010. Available at: http://www.cbc.ca/news/health/story/2010/09/08/fallopian-ovarian-cancer.html. Accessed May 12, 2013.
15. Reade CJ, Finlayson S, McAlpine J, Tone AA, Fung-Kee-Fung M, Ferguson SE. Risk-reducing salpingectomy in Canada: a survey of obstetrician-gynaecologists. J Obstet Gynaecol Can 2013;35(7):627–34.
16. Dubeau L. The cell of origin of ovarian epithelial tumors and the ovarian surface epithelium dogma: does the emperor have no clothes? Gynecol Oncol 1999;72(3):437–42.
17. Crum CP, Drapkin R, Miron A, Ince TA, Muto M, Kindelberger DW, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. Curr Opin Obstet Gynecol 2007;19(1):3–9.
18. Piek JM, Kenemans P, Verheijen RH. Intraperitoneal serous adenocarcinoma: a critical appraisal of three hypotheses on its cause. Am J Obstet Gynecol 2004;191(3):718–32.
19. Schubert EL, Lee MK, Mefford HC, Argonza RH, Morrow JE, Hull J, et al. BRCA2 in American families with four or more cases of breast or ovarian cancer: recurrent and novel mutations, variable expression, penetrance, and the possibility of families whose cancer is not attributable to BRCA1 or BRCA2. Am J Hum Genet 1997;60(5):1031–40.
20. Zweemer RP, van Diest PJ, Verheijen RH, Ryan A, Gille JJ, Simmons RH, et al. Molecular evidence linking primary cancer of the fallopian tube to BRCA1 germline mutations. Gynecol Oncol 2000;76(1):45–50.
21. Rosen B, Kwon J, Fung Kee Fung M, Gagliardi A, members of the Gynecology Cancer Disease Site Group. Management options for women with a hereditary predisposition to ovarian cancer. Program in evidence-based care. 2004. Evidence summary citation. Available at: https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34205. Accessed December 17, 2012.
22. Finch A, Shaw P, Rosen B, Murphy J, Narod SA, Colgan TJ. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. Gynecol Oncol 2006;100(1):58–64.
23. Powell CB, Kenley E, Chen LM, Crawford B, McLennan J, Zaloudek C, et al. Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: role of serial sectioning in the detection of occult malignancy. J Clin Oncol 2005;23(1):127–32.
24. Lee Y, Medeiros F, Kindelberger D, Callahan MJ, Muto MG, Crum CP. Advances in the recognition of tubal intraepithelial carcinoma: applications to cancer screening and the pathogenesis of ovarian cancer. Adv Anat Pathol 2006;13(1):1–7.
25. Colgan TJ, Murphy J, Cole DE, Narod S, Rosen B. Occult carcinoma in prophylactic oophorectomy specimens: prevalence and association with BRCA germline mutation status. Am J Surg Pathol 2001;25(10):1283–9.
26. Agoff SN, Mendelin JE, Grieco VS, Garcia RL. Unexpected gynecologic neoplasms in patients with proven or suspected BRCA-1 or -2 mutations: implications for gross examination, cytology, and clinical follow-up. Am J Surg Pathol 2002;26(2):171–8.
27. Medeiros F, Muto MG, Lee Y, Elvin JA, Callahan MJ, Feltmate C, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. Am J Surg Pathol 2006;30(0147–5185):230–6.
28. Mingels MJ, Roelofsen T, van der Laak JA, de Hullu JA, van Ham MA, Massuger LF, et al. Tubal epithelial lesions in salpingo-oophorectomy specimens of BRCA-mutation carriers and controls. Gynecol Oncol 2012;127(1):88–93.
29. Powell CB, Chen L-M, McLennan J, Crawford B, Zaloudek C, Rabban JT, et al. Risk-reducing salpingo-oophorectomy (RRSO) in BRCA mutation carriers: experience with a consecutive series of 111 patients using a standardized surgical-pathological protocol. Int J Gynecol Cancer 2011;21(5):846–51.
30. Lee Y, Miron A, Drapkin R, Nucci MR, Medeiros F, Saleemuddin A, et al. A candidate precursor to serous carcinoma that originates in the distal fallopian tube. J Pathol 2007;211(1):26–35.
31. Shaw PA, Rouzbahman M, Pizer ES, Pintilie M, Begley H. Candidate serous cancer precursors in fallopian tube epithelium of BRCA1/2 mutation carriers. Mod Pathol 2009;22(9):1133–8.
32. Folkins AK, Jarboe EA, Saleemuddin A, Lee Y, Callahan MJ, Drapkin R, et al. A candidate precursor to pelvic serous cancer (p53 signature) and its prevalence in ovaries and fallopian tubes from women with BRCA mutations. Gynecol Oncol 2008;109(2):168–73.
33. Jarboe E, Folkins A, Nucci MR, Kindelberger D, Drapkin R, Miron A, et al. Serous carcinogenesis in the fallopian tube: a descriptive classification. Int J Gynecol Pathol 2008;27(1):1–9.
34. Cass I, Holschneider C, Datta N, Barbuto D, Walts AE, Karlan BY. BRCA-mutation-associated fallopian tube carcinoma: a distinct clinical phenotype? Obstet Gynecol 2005;106(6):1327–34.
35. Woolas R, Jacobs I, Davies AP, Leake J, Brown C, Grudzinskas JG, et al. What is the true incidence of primary fallopian tube carcinoma? Int J Gynecol Cancer 1994;4(6):384–8.
36. Kindelberger DW, Lee Y, Miron A, Hirsch MS, Feltmate C, Medeiros F, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. Am J Surg Pathol 2007;31(2):161–9.
37. Przybycin CG, Kurman RJ, Ronnett BM, Shih Ie M, Vang R. Are all pelvic (nonuterine) serous carcinomas of tubal origin? Am J Surg Pathol 2010;34(10):1407–16.
38. Kuhn E, Kurman RJ, Vang R, Sehdev AS, Han G, Soslow R, et al. TP53 mutations in serous tubal intraepithelial carcinoma and concurrent pelvic high-grade serous carcinoma—evidence supporting the clonal relationship of the two lesions. J Pathol 2012;226(3):421–6.
39. Rodriguez-Burford C, Barnes MN, Berry W, Partridge EE, Grizzle WE. Immunohistochemical expression of molecular markers in an avian model: a potential model for preclinical evaluation of agents for ovarian cancer chemoprevention. Gynecol Oncol 2001;81(3):373–9.
40. Ilchmann G, Bergmann V. Histological and electron microscopy studies on the adenocarcinomatosis of laying hens [article in German]. Arch Exp Veterinarmed 1975;29(6):897–907.
41. Fathalla MF. Incessant ovulation—a factor in ovarian neoplasia? Lancet 1971;2(7716):163.
42. Casagrande JT, Louie EW, Pike MC, Roy S, Ross RK, Henderson BE. "Incessant ovulation" and ovarian cancer. Lancet 1979;2(8135):170–3.

43. Karst AM, Drapkin R. Ovarian cancer pathogenesis: a model in evolution. J Oncol 2010;2010:932371.

44. King SM, Hilliard TS, Wu LY, Jaffe RC, Fazleabas AT, Burdette JE. The impact of ovulation on fallopian tube epithelial cells: evaluating three hypotheses connecting ovulation and serous ovarian cancer. Endocr Relat Cancer 2011;18(5):627–42.

45. Vicus D, Shaw PA, Finch A, Rosen B, Murphy J, Armel S, et al. Risk factors for non-invasive lesions of the fallopian tube in BRCA mutation carriers. Gynecol Oncol 2010;118(3):295–8.

46. Saleemuddin A, Folkins AK, Garrett L, Garber J, Muto MG, Crum CP, et al. Risk factors for a serous cancer precursor ("p53 signature") in women with inherited BRCA mutations. Gynecol Oncol 2008;111(2):226–32.

47. Tone AA, Begley H, Sharma M, Murphy J, Rosen B, Brown TJ, et al. Gene expression profiles of luteal phase fallopian tube epithelium from BRCA mutation carriers resemble high-grade serous carcinoma. Clin Cancer Res 2008;14(13):4067–78.

48. Tone AA, Virtanen C, Shaw P, Brown TJ. Prolonged postovulatory proinflammatory signaling in the fallopian tube epithelium may be mediated through a BRCA1/DAB2 axis. Clin Cancer Res 2012;18(16):4334–44.

49. Tanner EJ, Chi DS, Eisenhauer EL, Diaz-Montes TP, Santillan A, Bristow RE. Surveillance for the detection of recurrent ovarian cancer: survival impact or lead-time bias? Gynecol Oncol 2010;117(2):336–40.

50. Tothill RW, Tinker AV, George J, Brown R, Fox SB, Lade S, et al. Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. Clin Cancer Res 2008;14(16):5198–208.

51. Somigliana E, Vigano P, Parazzini F, Stoppelli S, Giambattista E, Vercellini P. Association between endometriosis and cancer: a comprehensive review and a critical analysis of clinical and epidemiological evidence. Gynecol Oncol 2006;101(2):331–41.

52. Crum CP, Drapkin R, Kindelberger D, Medeiros F, Miron A, Lee Y. Lessons from BRCA: the tubal fimbria emerges as an origin for pelvic serous cancer. Clin Med Res 2007;5(1):35–44.

53. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 2004;3(8):711–5.

54. Landen CN, Birrer MJ, Sood AK. Early events in the pathogenesis of epithelial ovarian cancer. J Clin Oncol 2008;26(6):995–1005.

55. Lynch HT, Casey MJ, Snyder CL, Bewtra C, Lynch JF, Butts M, et al. Hereditary ovarian carcinoma: heterogeneity, molecular genetics, pathology, and management. Mol Oncol 2009;3(2):97–137.

56. Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2002;346(21):1609–15.

57. Gadducci A. Gynaecologic challenging issues in the management of BRCA mutation carriers: oral contraceptives, prophylactic salpingo-oophorectomy and hormone replacement therapy. Gynecol Endocrinol 2010;26(8):568–77.

58. Rebbeck TR, Lynch HT, Neuhausen SL, Narod S, Van't Veer L, Garber JE, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med 2002;346(21):1616–22.

59. 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(10):821–8.

60. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology 2007;69(11):1074–83.

61. Rocca WA, Bower JH, Maraganore DM, Ahlskog JE, Grossardt BR, de Andrade M, et al. Increased risk of Parkinsonism in women who underwent oophorectomy before menopause. Neurology 2008;70(3):200–9.

62. Rocca WA, Grossardt BR, Geda YE, Gostout BS, Bower JH, Maraganore DM, et al. Long-term risk of depressive and anxiety symptoms after early bilateral oophorectomy. Menopause 2008;15(6):1050–9.

63. Rivera CM, Grossardt BR, Rhodes DJ, Brown RD, Roger VL, Melton LJ, et al. Increased cardiovascular mortality after early bilateral oophorectomy. Menopause 2009;16(1):15–23.

64. Challberg J, Ashcroft L, Lalloo F, Eckersley B, Clayton R, Hopwood P, et al. Menopausal symptoms and bone health in women undertaking risk reducing bilateral salpingo-oophorectomy: significant bone health issues in those not taking HRT. Br J Cancer 2011;105(1):22–7.

65. Morelli M, Venturella R, Mocciaro R, Di Cello A, Rania E, Lico D, et al. Prophylactic salpingectomy in premenopausal low-risk women for ovarian cancer: primum non nocere. Gynecol Oncol 2013;129:448–51.

66. Sezik M, Ozkaya O, Demir F, Sezik HT, Kaya H. Total salpingectomy during abdominal hysterectomy: effects on ovarian reserve and ovarian stromal blood flow. J Obstet Gynaecol Res 2007;33(6):863–9.

67. Moller P, Borg A, Evans DG, Haites N, Reis M, Vasen H, et al. Survival in prospectively ascertained familial breast cancer: analysis of a series stratified by tumour characteristics, BRCA mutations and oophorectomy. Int J Cancer 2002;101(6):555–9.

68. Kwon JS, Tinker A, Pansegrau G, McAlpine J, Housty M, McCullum M, et al. Prophylactic salpingectomy and delayed oophorectomy as an alternative for BRCA mutation carriers. Obstet Gynecol 2013;121(1):14–24.

69. The Society of Gynecologic Oncology of Canada. GOC Statement regarding salpingectomy and ovarian cancer prevention. Available at: http://www.g-o-c.org/uploads/11sept15_gocevidentiarystatement_final_en.pdf. Accessed December 15, 2012.