Review Article

The clinical implications of new insights into the origins of epithelial ovarian cancer with emphasis on the British Columbia Ovarian Cancer Prevention Initiative

Dianne Miller

Division of Gynaecologic Oncology, Gordon and Leslie Diamond Health Care Centre, Vancouver, BC V5Z 1M9, Canada

ABSTRACT

In the last ten years our understanding of the origin of epithelial ovarian cancer has changed. This includes the realization that the majority of High Grade serous cancers originate in fallopian tube epithelium and the majority of endometroid and clear cell cancer arise in foci of endometriosis. These new insights have profound implications of both prevention and treatment.

Keywords: Clear cell cancers, epithelial cancers, epithelial ovarian cancer

INTRODUCTION

Ovarian cancer is the most common cause of death due to a gynaecologic malignancy. In addition, it is the fifth most common cause of cancer death in women. Historically, all epithelial ovarian cancers (EOCs) have been grouped together as one disease, and due to the fact they were all felt to have a common cell of origin, they were treated identically.

Recent advances in the morphologic classification of EOC have robustly identified five distinct histologic subtypes.[1,2]

These types are identified as:

- High-grade serous carcinoma (HGSC)
- Clear cell carcinoma (CCC)
- Endometrioid carcinoma
- Mucinous carcinoma
- Low-grade serous carcinoma.

The five subtypes vary with respect to presentation, natural history, response to therapy, prognosis and location of the cell of origin. By classifying them all as a single disease, as was done in the past, we may well have missed many opportunities in terms of prevention and treatment. Most large clinical trials have included multiple subtypes of epithelial cancer but due to the fact that the majority of these cancers were HGSCs, the responses of less frequent subtypes to therapies may have been lost in the data. An example is the fact that a significant proportion of mucinous tumours may overexpress Her-2 but because this is a very rare subtype the overall expression of Her-2 in EOC is extremely low resulting in a potential missed therapeutic opportunity for women with the infrequently occurring advanced mucinous tumours.[3]

Address for correspondence:
Dr. Dianne Miller, Division of Gynaecologic Oncology, Gordon and Leslie Diamond Health Care Centre, 6th Floor | Gynecology, 2775 Laurel Street, Vancouver, BC V5Z 1M9, Canada.
E-mail: dianne.miller@vch.ca

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In addition until recently, with the advent of a molecular classification, there was a high degree of inter-observer variability in the classification of EOC resulting in the misclassification of some tumours. We have now entered an era of sub-type specific classification, and both assigning and analysis of therapeutic interventions needs to reflect this.

In the last 10 years, our understanding of the cells of origin and the natural history of EOC has changed markedly. Previously, it was felt that all types of EOC developed from the cells of the ovarian surface epithelium (OSE) and underwent transformation to the various types of Müllarian epithelium.

In recent years, it has become apparent that the majority of high-grade serous tumours, (accounting for 70% of epithelial tumours) originate not from OSE but from the native serous epithelium of the fallopian tube.[4] In addition to this endometrioid and clear cell cancers, accounting for approximately 25% of epithelial malignancies of the ovary appear to have their origin in foci of endometriosis and not from OSE.

Low-grade serous tumours and mucinous tumours account for the remainder of the epithelial cancers and their origin at this time is less certain. These subtypes will not be discussed further in this paper.

Thus, it would appear that the majority of what was formerly known as EOC has cells of origin at sites other than the ovary. This paper focuses on the evidence for this new understanding and discusses the clinical implications in terms of prevention, screening and treatment. The paper will focus predominantly on HGS tumours as well as discussing some features of clear cell and endometrioid cancers.

HIGH-GRADE SEROUS TUMOURS

Seventy percent of EOCs have HGSC histology. Almost all HGSCs have TP53 mutations which seem to occur as early events in disease progression. Approximately, half of the HGSCs have BRCA dysfunction, through a combination of germline and somatic mutations or epigenetic silencing.[5] TP53 mutations and BRCA deficiency lead to incompetence in DNA repair, making HGSC highly responsive to chemotherapy, often repeatedly.[6] However, the majority of patients will develop recurrences, ultimately developing disease resistance and succumbing to their disease.

Cancer of the fallopian tube [Figure 1] has long been considered the rarest of gynaecologic malignancies. In most standard textbooks, it is stated that the fallopian tubes account for <1% of gynaecologic cancers. We now have good evidence to show that as opposed to being a rare event, the majority of high-grade serous cancers of the ovary, in fact, arise in the distal end of the fallopian tube. These lesions can shed cancer cells into the peritoneal cavity early in their natural history and hence generally present with widespread metastatic disease. Because the fallopian tube is found adjacent to the ovary anatomically and because ovarian involvement is an early event and is often massive in the natural history of the disease this was long felt to be the anatomical site of origin.

An important question when discussing the natural history of any cancer is: 'Is there a precursor lesion?' We know that cervical cancer is preceded by cervical intraepithelial neoplasia, breast cancer by ductal carcinoma *in situ*, colon cancer by atypical adenomas but until recently, in spite of years of searching no precursor lesion had been identified for HGS cancers in the ovary. This changed when pathologists started to systematically examine the fallopian tube in women undergoing prophylactic bilateral salpingo-oophorectomy for germ cell BRCA mutations. With the identification of BRCA 1 and 2 mutations and the recommendations for prophylactic surgery to prevent this cancer in known carriers, it became apparent that the earliest lesions were found predominantly in the fallopian tube, not the ovary. Most modern series, with careful sectioning of the fallopian tubes, show more than 90% distal fallopian tubal origin for high-grade serous cancers in the BRCA population. We now know that the serous tubal intraepithelial carcinoma (STIC) is the precursor lesion to HGS cancers [Figure 2].

There is increasing evidence that the same is true for non-BRCA tumours as well. In our own early series from our institution, careful examination of the fallopian tubes in unselected sequential patients with advanced HGS tumours demonstrated that we were able to identify a presumptive fallopian tube precursor in at least 75% of cases.[7,8] In all of these cases, the precursor lesion was identified only unilaterally in the tube and on the side of the largest ovary.[9]

More recently in examining opportunistic salpingectomy specimens, all occult cancers and STICs have arisen in the fallopian tubes not the ovary. Figure 2 shows the presence of an STIC. This lesion has all of the mutations expected in an HGS cancer. When this lesion is found in the tube, the patient requires a full staging procedure as even at this early state there can be the shedding of cells into the peritoneal cavity, and there are many reports of recurrence post STIC usually in patients who have not been staged.[10]

The clinical implications in terms of prevention and screening are clear. Figure 3 shows that in spite of several advances in treatment there have been only small gains in progression-free interval and overall survival for this population of patients. In addition, three large screening studies have failed to show any substantial impact on either early diagnosis or mortality and come at the cost of many potentially morbid and unnecessary interventions.[11-13] The reason for the failure of these screening interventions now seems clear. Whilst we thought that these cancers originated in the ovary, the rationale for using imaging and tumour markers made sense to a degree based on the assumption that there was a possibility to diagnose cancer at an earlier and hence more curable stage if it could be successfully imaged. We now know that with the origin in the fallopian tube the reality is that once there is ovarian involvement we are already dealing with the metastatic disease. The Ca-125 tumour marker though useful in monitoring treatment has been less useful in screening due to the fact that it is elevated in many if not all situations where there is disturbance/disruption of the peritoneum. The origins from the fallopian tube though have given rise to some tantalizing and potentially new approaches to screening. In the absence of tubal ligation, the fallopian tube and its secretions are usually accessible through the lower genital tract, and it is at least theoretically possible that in the future there may be the development of tests looking for unique proteins or mutations found in the early precursor lesions found in the tube. At this point, this is highly speculative and due to the relative rarity of HGS cancers (1/70–80 lifetime risk) it is unlikely that there will be the development of broad population-based testing anytime soon.

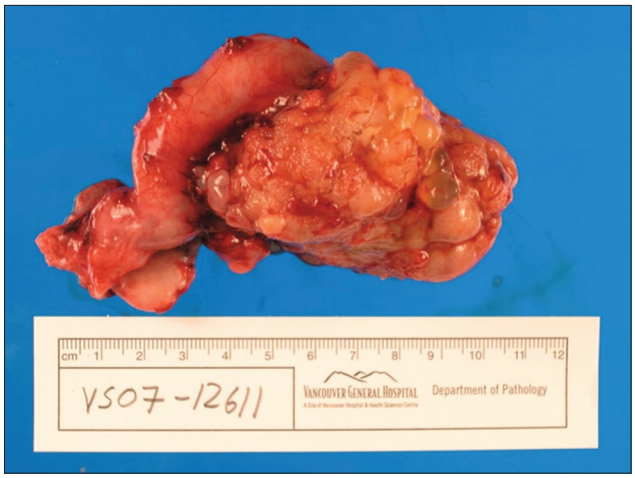

Figure 1: Cancer arising from the fallopian tube with normal ovary to the right of the photograph

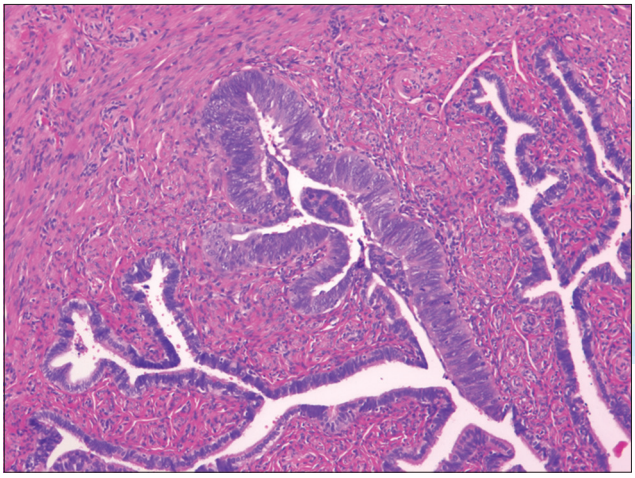

Figure 2: Serous tubal intraepithelial carcinoma discovered with careful sectioning of the fallopian tube

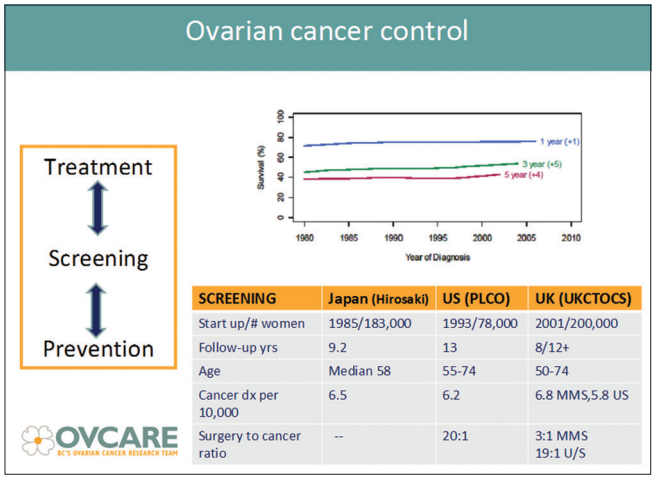

Figure 3: Current state of treatment and screening for high-grade serous cancers

Prevention is another story. With the knowledge that the majority of cases of this lethal cancer arise in the distal end of the fallopian tube, this gives us the potential to consider new possibilities for prevention. We have known for many years that the fallopian tube plays a role in decreasing the risk of ovarian cancer. In the past, we have not understood the pathophysiology of this protection. With our new understanding that ovarian cancer is really five unique types of cancer the roll of tubal ligation is becoming clearer. Figure 4 shows a table from an article by Sieh[14] analysing the effect of tubal ligation on the incidence of various subtypes of ovarian cancer. The majority of the benefit accrues to the clear cell and endometrioid subtypes and not the serous subtypes. The reasons for this will be discussed later in this paper. Suffice it to say tubal ligation provides only a modest reduction in HGS cancers. This is likely because the high-risk portion of the fallopian tube, namely the ampulla and fimbriated end remains with the patient following tubal ligation.

Data from our centre showed that almost 20% of women who developed HGS cancer in our province had

undergone a hysterectomy for benign disease prior to their diagnosis. This led us to surmise that in this 20% of women there would have been an opportunity to remove the distal fallopian tube and potentially prevent the development of this cancer. We also know that in our population a further 20% of women will undergo the procedure of tubal ligation, or surgery for benign ovarian cysts past the time of desired fertility further increasing the number of women in whom there would be a potential opportunity to remove the distal end of the fallopian tube.

In addition, we were able to determine that in our population over 20% of the women diagnosed with this cancer had a germline mutation in BRCA (internationally, this number varies from a low of about 10% in some populations to highs of almost 25% in other populations, but has steadily increased over the years with the improvements in testing).[15] By implementing a policy of BRCA testing all women diagnosed with HGS cancers, we would have the opportunity to identify unaffected at-risk women in the population, (the first and second-degree relatives of known carriers) and offer genetic testing and if positive, proven effective risk-reducing surgery.[16]

In recent years, the cost of germline testing has decreased markedly, and we can now conceive of time when it may be possible to offer population-based testing, with testing of all women for mutations in BRCA 1 and 2 (not to mention the Lynch genes). With an increase in the sophistication of the public's knowledge the opportunities for prevention of hereditary cancers is on the horizon.

This meant that in almost half of women there would be an opportunity to potentially prevent the development of this lethal cancer.[17] 20% through routine removal of the fallopian tube at the time of hysterectomy, 10 - 20% through the removal of the fallopian tube in lieu of tubal ligation or at the time of surgery for benign disease post child-bearing and up to 20% through the identification of women at high risk based on BRCA testing.

Armed with this knowledge, the province of British Columbia in Canada launched the first population-based ovarian cancer prevention program based on 'opportunistic salpingectomy' and BRCA testing of affected women.

The following table summarizes the elements of the British Columbia Ovarian Cancer Prevention Initiative and the expected outcomes of these interventions [Figure 5]. All practicing gynaecologists were provided with detailed references and educational resources including multiple video vignettes. All of this educational material can be found online at www.ovcare.ca.

Our first objective was to demonstrate that the program was safe in terms of not increasing any indicator of perioperative morbidity. A paper published by our group[18] and another by Canadian Partnership Against Cancer[19] demonstrated no increase in hospital stay, blood loss or re-admission rates and also documented that there was only minimal increase in surgical time.

In addition, it has been noted that the fallopian tube is not infrequently the source of additional problems if left *in situ* at the time of a hysterectomy [Figure 6].

Definitive data on ovarian function will have to wait for long-term follow-up of this strategy. A paper by Morelli *et al*. as well as our own data shows that thus far there does not seem to be any identifiable effect. An interesting but unanticipated outcome of offering opportunistic salpingectomy to women is that more women in the peri-menopausal age group are opting to keep their ovaries *in situ* and just have the tubes removed. The long-term effects of this change will

Subtype-specific odds ratios for invasive epithelial ovarian cancer associated with tubal ligation

Histological subtype	Cases (n=7451)	Adjusted* OR (95% CI)
Serous	4772 (64.0)	0.81 (0.74-0.88)
High Grade	4444	0.81 (0.74-0.89)
Low Grade	328	0.83 (0.60-1.16)
Endometrioid	1317 (17.7)	0.62 (0.48-0.80)
Clear Cell	754 (10.1)	0.48 (0.40-0.58)
Mucinous	608 (8.2)	0.52 (0.41-0.67)

* Conditional logistic regression stratified by site and age (5-year groups) and adjusted for age (continuous), race/ethnicity, OC use, and parity.

Seih, Salvador et al, Int J of Epidemiology 2013

Figure 4: Subtype specific protection from tubal ligation

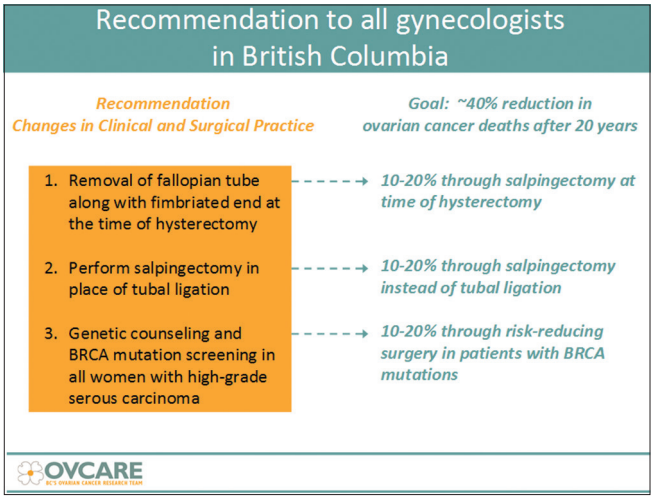

Figure 5: British Columbia Ovarian Cancer Prevention Initiative and expected outcomes

be interesting especially in terms of data from the 'nurses' health study'[20] demonstrating the adverse effects of premature oophorectomy in terms of other non-malignant health outcomes.

The launch of our program garnered international interest, some skeptical but mostly supportive, and in the intervening 5 years since our launch many jurisdictions have developed guidelines and made similar recommendations for women undergoing benign gynaecologic surgery. We estimate that given the fact that the majority of HGS cancers occur in women in their 50's and 60's and that the majority of hysterectomies for benign disease (usually leiomyomas, abnormal bleeding, endometriosis, etc.) occur in women in their 30's and 40's it will be 15 - 20 years before we see an effect of this change in surgical practice on the incidence of HGS cancers.

With respect to this, there are some tantalizing clues that we are on the right track. A study by Gilks *et al*.[21] (in press) demonstrates that all of the occult cancers discovered since the program began have involved the tube and that only one has involved the tube and adjacent ovary.

CONCLUSION

'Opportunistic salpingectomy' and liberal BRCA testing have the potential to prevent up to 50% of HGS cancers with the potential to markedly decrease both the incidence and mortality from this disease.

Clear cell and endometrioid epithelial cancers

CCCs and endometrioid carcinomas are the second and third most common epithelial cancer subtypes occurring in the ovary. These cancers account for almost a quarter of the epithelial malignancies. They tend to occur in a younger age group. These cancers have now been convincingly shown to arise predominantly in association ovarian foci of endometriosis.[22,23] The cancers often develop on the interior aspect of endometriomas and tend to be a low stage at diagnosis in contrast to the HGS tumours. If they are a low stage they have a good prognosis and may not require any adjuvant treatment. If they are an advanced stage, the prognosis is poor.

Clear cell cancers, in particular, do not have the same response rates to chemotherapy and once advanced have a very poor prognosis. These cancers may be more sensitive to radiotherapy than HGS.

Sieh *et al*. showed that tubal ligation has its largest effect on preventing the development of these two subtypes of epithelial cancer. Figure 7 illustrates the presumptive roll of the tube in the prevention of these cancers.[24] Retrograde menstruation has long been implicated as a source for endometriosis, and tubal ligation will prevent this.

These cancers can be shown to have mutation profiles unique from HGS such as mutations ARID 1A and a lack of p53 mutations.[25] Furthermore, that these mutations can be identified in foci of endometriosis adjacent to the tumour indicates that they may be an early event in the malignant transformation.[26]

Several important questions remain. Endometriosis is a relatively common benign gynaecologic condition. Hence what are the risk factors for the development of cancer in endometriosis? Can we identify features in endometriosis which will predict the subsequent development of malignancy? Though malignancy can occur in non-ovarian foci of endometriosis this is a very rare event as compared to the development

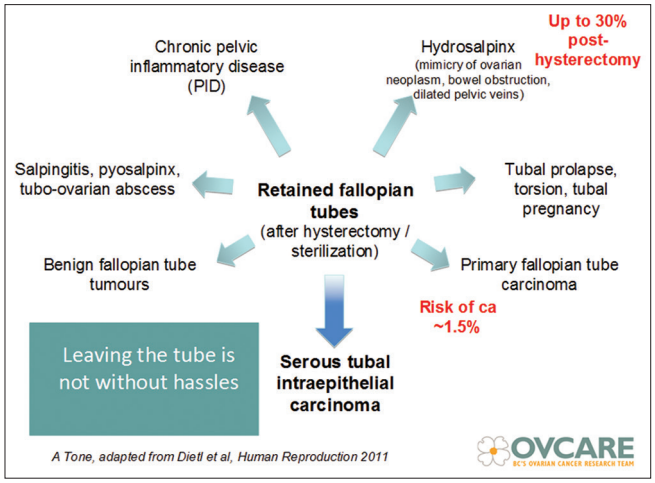

Figure 6: Fallopian tube post-hysterectomy: Potential complications

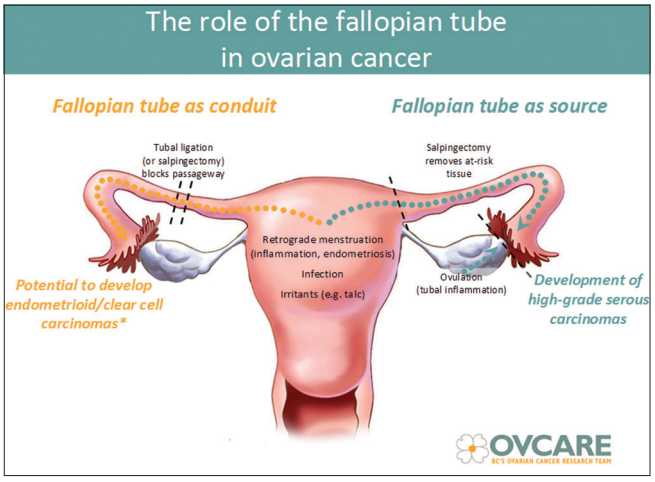

Figure 7: The role of the fallopian tube in the prevention of 'ovarian cancer'

of cancer in endometriomas, but why, this is still not known?

SUMMARY

The last 10 years has seen a sea change in our understanding of both the origins and the pathophysiology of EOC. Some have suggested that it is time to consider changing the names of these to reflect the new insights into their tissues of origin. Thus, fallopian tube cancer would go from a very rare, <1% of gynaecologic malignancies, to the most common lethal gynaecologic cancer. It is apparent, however, that some of these cancers do originate on/in the ovary and or in the pelvic peritoneum, perhaps in sequestered fragments of fallopian tube epithelium and or endosalpingiosis. In my opinion, better suggestion would be to classify the tumours by their type based on their molecular profile, a technique which is becoming more robust. This will allow for a better comparison of therapeutic interventions. For the endometrioid and clear cell tumours, it is clear that these are a distinct entity from HGS and more akin to endometrial cancer and with their own unique mutation profiles.

For the 1st time, we are in a position to potentially prevent a large proportion of the HGS cancers and start to understand the role of endometriosis in the development of the endometrioid and clear cell cancers. The next 15 years will determine if 'opportunistic salpingectomy' and BRCA testing can reap the benefits we expect.

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Conflicts of interest

There are no conflicts of interest.

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