SCREENING PORTFOLIO

Ovarian Cancer Screening

Expert Panel: Summary of Existing and New Evidence

October 4, 2011

CANADIAN PARTNERSHIP AGAINST CANCER
PARTENARIAT CANADIEN CONTRE LE CANCER

ANTICIPATORY SCIENCE
a summary of existing and new evidence

Table of Contents

Expert Panel Members

Dr. Barry Rosen – co-Chair
barry.rosen@uhn.on.ca

Professor of Obstetrics and Gynecology,
University of Toronto
Princess Margaret Hospital, Toronto
Member, Society of Gynecologic Oncology of
Canada

Dr. Verna Mai – co-Chair
verna.mai@partnershipagainstcancer.ca

Chair, Screening Action Group,
Canadian Partnership Against Cancer

Ms. Elizabeth Ross
eross@ovariancanada.org

Chief Executive Officer,
Ovarian Cancer Canada

Dr. Brenda Woods
bwood@tegh.on.ca

Chief of Obstetrics and Gynecology, Medical
Co-Director of the Maternal Newborn Council,
Toronto East General Hospital

Dr. David Huntsman
dhuntsma@bccancer.bc.ca

Associate Professor, Department of Pathology &
Laboratory Medicine, University of British
Columbia
BC Cancer Agency

Dr. Gennady Miroshnichenko
Gennady.Miroshnichenko@uhn.on.ca

Clinical Fellow, Division of Gynecologic
Oncology,
Princess Margaret Hospital, University Health
Network, Toronto

Dr. Anthony Miller
ab.miller@utoronto.ca

Professor Emeritus, Dalla Lana School of Public
Health,
University of Toronto

Dr. Alicia Tone
alicia.tone@utoronto.ca

Post-doctoral Fellow,
Princess Margaret Hospital & Samuel Lunenfeld
Research Institute, Toronto

Dr. Walter Rosser
rosserw@queensu.ca

Professor, Department of Family Medicine,
Queen's University

Ms. Fran Turner
fturner@ovariancanada.org

National Program Director
Ovarian Cancer Canada

Dr. Clare Reade
clarereade@gmail.com

Resident in Obstetrics and Gynecology,
McMaster University

Dr. Katharina Kieser
kkieser@dal.ca

Associate Professor, Gynecologic Oncology
Faculty of Medicine,
Dalhousie University

Dr. Bernard Candas
bernard.candas@partnershipagainstcancer.ca

Senior Scientific Lead, Analytic Networks,
Surveillance Portfolio,
Canadian Partnership Against Cancer

Summary Statement of the Panel

There is considerable interest in screening for ovarian cancer because the disease is highly lethal and currently most often detected in its advanced stages. If screening could detect more early-stage ovarian cancers, the hope is that survival rates would improve. However, ovarian cancer is a complex disease and not all of its histologies act in the same way. While some are detected more often in early stage, serous histology, the most common ovarian cancer usually presents as Stage 3 or 4.

The evidence to date has not demonstrated that ovarian cancer screening reduces mortality from ovarian cancer. The most recent study, conducted by the U.S. National Cancer Institute's Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, evaluated transvaginal ultrasound and CA 125 tests in screening post-menopausal women aged 55 to 74 for ovarian cancer. The study involved 78,216 women of which 39,105 were screened (the study arm) and 39,111 women were followed routinely (control arm). Women were offered annual testing over 6 years and were followed for a total of 13 years.

212 women in the study arm and 176 in the control arms were found to have ovarian cancer. There were 118 deaths from ovarian cancer in the study arm compared to 100 in the control arm. The authors of the study concluded that screening with CA 125 and TVUS did not reduce ovarian cancer mortality.

The surgical complication rate as a result of a false positive test is 20.6 per 100 procedures in the PLCO study. This complication rate is an important factor when evaluating outcomes for ovarian cancer screening. This rate of complication would only be acceptable if mortality from ovarian cancer was substantially reduced.

This panel believes that this study was very well conducted and evaluated a large population. Based on this and other evidence sited in this report we do not recommend routine ovarian cancer screening for the general population at this time.

Purpose

The potential for mortality reduction from cancer screening makes efficacy results from screening trials highly anticipated. The publication of such results are of interest to women in Canada, medical specialty groups and health ministries, creating the need for timely reviews of the publications as well as of related articles by health-policy advisers involved in cancer control. The Canadian Partnership Against Cancer has brought together a panel of experts to review and summarize the relevant information related to ovarian cancer screening, including the recent publication of the U.S. National Cancer Institute's Prostate, Lung, Colorectal, Ovarian (PLCO) Cancer Screening Trial mortality results (released June 4, 2011).

Several screening studies have been published in the past evaluating ovarian cancer screening, including three randomized controlled trials – PLCO, the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) and Japan's Shizuoka Cohort study of Ovarian Cancer Screening Trial. This document summarizes key features of these trials, providing clinical context, helping to fill in knowledge gaps and set future direction.

This document is not intended to provide definitive answers or clinical and/or policy recommendations. The views expressed herein represent the views of the Ovarian Cancer Screening Expert Panel.

Material appearing in this report may be reproduced or copied without permission. However, the following citation to indicate the source must be used:

Canadian Partnership Against Cancer, Ovarian Cancer Screening Expert Panel. Ovarian Cancer Screening Expert Panel: Summary of Existing and New Evidence. Toronto: Canadian Partnership Against Cancer; 2011.

Summary

Ovarian cancer affects 2500 women each year in Canada and approximately 60% (1500) of them will die from it. It has very high fatality rates for any cancer and is the 5th leading cause of cancer death for women.

Most women (70%) are diagnosed after the cancer has spread when it is either stage 3 or 4. Survival from advanced stages is only 15-20%. When detected earlier, as stage 1 or 2 survival rates are much higher, 90% for stage 1 and 66-69% for stage 2. The reason that most women with ovarian cancer present in advanced stages is that it rarely produces symptoms in which would alert a woman or her doctor when it is in its early stages.

Screening has been proposed as a strategy to detect ovarian cancer in early stages which in turn should improve cures rates from it. Several studies over the past 20 years have been published demonstrating potential benefit through screening with a blood test CA 125 and transvaginal/pelvic ultrasound. Until publication of the PLCO study abstract at ASCO (American Society of Oncology) in 2011 none of the previously published studies evaluated mortality (end point of interest) from ovarian cancer.

The PLCO study has just presented results from its multi-year randomized controlled trial which was initiated in 1993. This trial evaluated annual screening with both CA 125 and transvaginal ultrasound in women aged 55-74 years. Its primary aim was to determine if screening would reduce mortality from ovarian cancer.

In a previous publication (Onstet &Gynecol 113:775 2009) this group reported details of the study including demographics, number of women undergoing annual screening, number of positive tests, number of cancers detected, and number of surgeries performed to detect them.

In their most recent presentation they report on their primary end point, mortality from ovarian cancer. 78,216 women aged 55-74 years participated in the PLCO study comparing CA 125 and transvaginal

ultrasound (TVUS) to routine care. 39,105 were randomized to the study arm (CA 125 & TV US) and 39,111, the control arm, were randomized to routine care.

212 women in the study arm were detected with ovarian cancer compared to 176 in the control arm. After follow-up of 13 years the study arm had 118 deaths compared to 100 in the control arm for a mortality ratio of 1.18 (95%CI 0.91-1.54) and this difference is not statistically significant.

3,285 women underwent surgery for false positive testing and of these 166 had at least one serious complication. In their 2009 paper the authors provided data on the number of surgical procedures needed to detect each cancer. Phrased another way, 19 women underwent surgery for every cancer that was detected.

The study authors state that screening with CA125 and TVUS did not reduce ovarian cancer mortality when compared to the general population. As well there was evidence of harm from diagnostic evaluation of false positive testing.

The Society of Gynecologic Oncologists of Canada (GOC) believes that this study was very well conducted and evaluated a large population over many years. The paper from this study has not yet been published however based on the ASCO abstract and presentation GOC accepts the findings from this study and does not recommend women undergo screening with CA125 and TVUS for ovarian cancer.

Clinical Context and Introduction

Burden of Disease

Ovarian cancer is the fifth leading cause of cancer death among women in Canada. In 2010, it is estimated that 2,600 women will be diagnosed with ovarian cancer and 1,750 will die from the disease (Table 1). The average age of diagnosis is 58 with approximately two-thirds of all patients being over 55.

Table 1: Incidence and Mortality by Province[1]

Province	NL	PE	NS	NB	QC	ON	MB	SK	AB	BC
Incidence	25	10	65	65	690	1,050	95	70	180	300
Mortality	30	5	60	45	390	710	65	55	150	240

The cure rate for ovarian cancer is as high as 80 per cent to 90 per cent for Stage 1 and 66 per cent to 69 per cent for Stage 2 cancers.[2-4] In general, however, ovarian cancer has few or no symptoms when it is in Stage 1 or 2 because symptoms usually manifest when the cancer has spread to other intra-peritoneal organs.

The lack of symptoms in early stages makes early detection very difficult. There have been attempts to identify specific symptoms to aid in early detection of the disease, with little success. In more advanced stages, the cure rate is only 15 per cent to 20 per cent. Seventy per cent of ovarian cancers are detected only when they have advanced to Stage 3 or 4.[2-4]

Ovarian Cancer Types

There are several different types of ovarian cancer including germ cell, stromal cell and epithelial cell. The cancers referred to in this summary are epithelial in origin, the most common and usually affecting women over age 35.

However, epithelial tumours are not uniform. There are five different histologic subtypes, and each subtype contains a group of tumours classified as borderline or low-malignant potential. These latter group tumours are more invasive than benign tumours but also much less aggressive than the more common invasive epithelial tumours.[2,3,5-7]

There is no consensus on how quickly ovarian tumours develop or progress.[7] In the past, all ovarian cancer histologic subtypes were grouped together and studied as one disease. With better understanding in recent years of the different histologic subtypes, there is recognition that they are distinct in their natural history and presentation. For example, serous histology presents in advanced stages (3 or 4) 80 per cent of the time, whereas endometrioid cancers are detected 85 per cent of the time in early stages (1 or 2). See Table 2 for presentation of different histologic subtypes.[6]

Table 2: Ovarian Cancer Histological Subtypes[6]

Histology	Per cent presenting as stage 1 or 2 cancers	Per cent presenting as stage 3 or 4 cancers
Serous	15	85
Endometrioid	85	15
Clear cell	80	20

Implications for Screening Strategies

Screening is one potential strategy for improving ovarian cancer outcomes. Effective screening could move detection from advanced to early stages where cure rates are much better. If ovarian cancer screening could result in a shift in early detection from 30 per cent to 70 per cent, the overall cure rate for ovarian cancer could potentially increase from 30 per cent to 65 per cent. The requirements of an effective screening test are outlined in the appendix.

Prevalence of the disease is an important factor affecting the effectiveness of screening. Screening tests perform more accurately when applied to cancers that have a higher prevalence in a population — for example, breast cancer.[4] Because ovarian cancer occurrence is relatively low, screening tests perform less well.[3,4] The absolute impact on disease burden will also be relatively small in low-prevalence diseases, even if a reduction in mortality from screening can be shown.

The multiple histologic subtypes of ovarian cancer and unique natural history and behaviour patterns for each type also create a challenge. For example, if screening detects only endometrioid or clear-cell cancers, but not other subtypes, or the tests largely miss the early stages of more fatal cancers, its effectiveness for the population overall on early detection will be limited.

Therefore, evaluation of screening strategies needs to take subtyping into account. If a screening test does not detect a high proportion of the more aggressive types of ovarian cancer at a curable stage, its utility is questionable.

Another factor that influences screening is the extent of understanding related to ovarian cancers' cells of origin. For a long time, researchers believed that ovarian cancers developed from the ovary's surface epithelial cells. The theory was that these cells would undergo a transformation into cancer and take on a specific histologic subtype. Recent studies,[1,8-11] however, provide emerging evidence that the serous histologic subtypes arise not from the ovarian epithelium but from the fallopian tube. If this is correct — and evidence is accumulating quickly — screening tests that evaluate only the ovary will miss serous ovarian cancers.[1,8,9,11]

Family history of cancers is also important when evaluating screening studies. Those women with a BRCA1 or 2 gene mutations are at an increased risk of developing ovarian cancer ranging from 25 per cent to 45 per cent, as are women with mismatching repair gene mutations whose risk of ovarian cancer is increased to 12 per cent. While screening is a potential advantage in these groups (because prevalence of ovarian cancer is higher) it has not yet been shown to be effective using available tests.[12]

Tests Studied in Ovarian Cancer Screening Trials

The two tests that have been used for ovarian cancer screening to date are a blood test, CA 125, and a pelvic ultrasound. However, neither of these, alone or in combination detected the cancer at an earlier, more curable stage.

CA 125, cancer antigen 125 or carbohydrate antigen 125, is a protein that in humans is encoded by the mucin 16 (MUC 16) gene. CA 125 has found its application as a tumour marker that may be elevated in some patients' blood, suggesting the presence of some type of cancer.

In 79 per cent of women with ovarian cancer, the CA 125 is increased and easily detected in a blood sample. For these reasons, it has been used as a screening test. However, it is raised in only 50 per cent of women with early-stage ovarian cancer and is also elevated in a number of other states, such as menstruation, endometriosis and appendicitis.[13]

Pelvic ultrasound, trans-abdominal and trans-vaginal, has also been used as a screening test. The trans-abdominal approach uses gel with the ultrasound probe over the abdomen's lower portion to take images of the uterus, bladder, fallopian tubes and ovaries. The transvaginal (TVU) approach requires a specialized probe to be placed in the vagina with images taken from its top.

In many situations, ovarian cancers develop cysts or masses on the ovary. In these cases, an ultrasound is useful for detection. However, for the ultrasound to be an effective detection measure, these masses or cysts need to develop before the cancer spreads. Another complication is that the primary cancer can spread before it is large enough to be detected by ultrasound. Speed of growth and tumour spread, as well as variability between histologic subtypes, makes ultrasound effective for some, but not all, histologies.[3]

Women who are found to have an increased CA 125 or an abnormality on pelvic ultrasound require further tests to determine whether these results are produced by ovarian cancer or other causes. These additional tests can include repeat CA 125 to determine whether it is continuing to increase or not, or a repeat ultrasound to determine whether the cyst has changed. If, after these further investigations, there is still a concern that there may be a malignancy, then surgery is required.

When surgery is indicated, it needs to be performed for both diagnostic and therapeutic reasons. Diagnosis includes obtaining tissue for histology and staging. The diagnostic component of surgery includes removal of the primary tumour and will often also require removal of the other ovary and uterus. When the cancer is apparently limited to the ovary, it is also necessary to remove the omentum, pelvic and para aortic lymph nodes and biopsy any suspicious nodules wherever they are within the abdomen. If the cancer has spread beyond the ovary the therapeutic part of surgery involves removal of as much of the tumour as possible and this is referred to as debulking. When staging and debulking surgery are performed comprehensively the individuals' outcome is optimized.

Randomized Control Trials: Ovarian Cancer Screening

Currently three randomized controlled trials of ovarian cancer screening are underway. The first trial, from Japan, concerns outcomes pertaining to cancer incidence in the screening and control arms after a mean follow-up of 9.2 years.[14] The PLCO trial published results for its initial round of screening in 2005 and from four rounds in 2009.[15,16] In 2009, the UKCTOCS also published results of its prevalence screen round.[17] Table 3 shows the highlights of each of these three trials.

Table 3: Key Features of Ovarian Cancer Screening Trials

Features	SKSOCS[14]	PLCO[16]	UKCTOCS[17]
Trial	Shizuoka Cohort Study of Ovarian Cancer Screening	Prostate, Lung, Colorectal, Ovary Screening	U.K. Collaborative Trial of Ovarian Cancer Screening
Start date	1985	1993	2001
Accrual	82,487	68,558	202,638
Duration of follow-up	Mean 9.2 years	Median 11.5 years	3-7 years
Randomization method	Women who visited one of 212 hospitals if asymptomatic were invited; randomized 1:1 intervention vs. usual care; no mention of consent	Individual consent	Identified from GP registers. Written consent. Allocation after eligibility confirmed. Ratio 2 control: 1 MMS, 1 USS.
Location	Shizuoka District, Japan	10 centres, United States	13 regional centres, United Kingdom
Age group	Range not given; post-menopausal. Median age 58 years.	55-74 years	50-74 years
Screen design	Annual TVU (until 1990 trans-abdominal) and CA 125 up to five screens	Annual CA 125 screen for six years and annual TVU for four years	MMS: Annual CA 125 until Dec. 31, 2011 Those deemed at elevated risk of ovarian cancer receive TVU USS: Annual TVU until Dec 31, 2011 Those abnormal have repeat TVU
CA 125 level for referral	Greater than 35 units/mL	35 units/mL or more	According to a risk algorithm

Features	SKSOCS[14]	PLCO[16]	UKCTOCS[17]
Follow-up action	Referral to gynecologist	Patient and physician decide on the next step which, for most, is referral to a gynaecologist	Assessment by a designated clinician
CA 125 above threshold on first screen	7.8 per cent	1.4 per cent	0.3 per cent (after full algorithm applied – i.e., referred for surgery)
Positive TVU on first screen	4.7 per cent	4.6 per cent	3.8 per cent (after full algorithm applied; i.e., referred for surgery)
Positive predictive value of abnormal CA 125 result	0.8 per cent	3.2 per cent at first screen	35.1 per cent at first screen (MMS)
Positive predictive value of abnormal TVU	1.2 per cent	0.9 per cent at first screen	2.8 per cent at first screen (USS)
Positive predictive value of both TVU and CA 125	0.6 per cent	1.1 per cent at first screen (1.0-1.3 per cent subsequently)	N/A
Cancer diagnosis rate (excluding borderline)	6.5/10,000 first screen (not clear if borderline excluded)	6.2/10,000 first screen (4.7 to 5.9 subsequently)	First screen: MMS: 6.8/10,000 USS: 5.0/10,000
Stage distribution in per cent	I II III IV Screened: 51 11 31 6 Control: 38 6 50 6 (Screened includes 27 screen-detected and eight interval cancers vs. 32 control)	I II III IV NA Screened: 15 8 56 19 2 Control: 12 12 46 30 1 (Clinical stage)	I II III IV NA MMS: 41 6 53 0 0 USS: 42 8 42 8 0 Control: NA
Additional comments	Recruitment continued to 1999. Cancers identified by linkage to cancer registry.		Differential withdrawal, 562 from MMS group, 2,409 from USS group, none from control; i.e., from intention to screen analysis.

CA 125: Cancer antigen 125 or carbohydrate antigen 125
TVU: Transvaginal Ultrasound
MMS: Multimodal screening
USS: Ultrasound screening

Only the PLCO trial has reported on mortality outcomes and these results are shown in Table 4.

Table 4: Mortality Outcomes: PLCO[18]

Group	Number	Number with ovarian cancer	Number died from ovarian cancer
Screened	39,105	212	118
Control	39,111	176	100

Diagnosis rate ratio: 1.21 (95%CI 0.99-1.48)
Mortality ratio: 1.18 (95%CI 0.91-1.54)

The PLCO study reported on procedures for 3,285 false positive tests. There were 1080 surgical procedures with 163 of the 1,080 experiencing major complications including infection (89), cardiopulmonary (31), surgical (63) and other (31). The rate of complications was 20.6 per 100 procedures.

Risks and Benefits of Ovarian Screening

Currently, the evidence shows that cancer screening has little impact on ovarian cancer mortality.[16] Additional evidence from the three randomized trials discussed above is anticipated to be available over the next few years. Evidence has also been accumulating on the potential harms caused by routine screening for ovarian cancer. These harms, including anxiety and repeat testing, result from the follow-up that is required for women who have an abnormal screening result. Besides repeat CA 125 and/or ultrasound testing, such follow-ups may include surgery (laparoscopy or laparotomy) for diagnosis.

According to the PLCO trial results, approximately 20 surgeries are performed per invasive cancer diagnosed as a result of screening with CA 125 or ultrasound.[16] In the U.K. trial, the number of surgeries per invasive cancer diagnosed was lower when a multimodal screening strategy was employed (sequential screening with CA 125 as the initial and subsequent test and possible ultrasound, depending on the initial test results). In fact, in the U.K. cancer multimodal screening arm, one cancer was detected for each of 2.9 surgeries vs. one for 18.8 in the ultrasound arm.[17]

The predictive values (i.e., the percentage of positive screening tests that resulted in an invasive cancer being diagnosed) of the screening tests evaluated in the trials are low, with estimates of 0.7 per cent to

1.1 per cent for transvaginal ultrasound and 2.1 per cent to 3.2 per cent for CA 125 as reported from the PLCO trial.[16] This means that the vast majority of women who have an abnormal screen do not have invasive ovarian cancer diagnosed even after further assessment and surgeries.

In addition to the unnecessary surgeries, there is the harm of increased anxiety originating from an abnormal screening test result. Currently, the evidence indicates that screening is likely to result in more harm than good. Until more definitive evidence of benefit becomes available, screening should not be implemented on a population basis.

Education

Since ovarian cancer symptoms can mimic less harmful conditions, the public and health-care professionals need to be better educated about the disease, especially in the absence of an effective screening test. A 2005 national survey found that 96 per cent of women could not identify a combination of the most common symptoms of ovarian cancer. Furthermore, since ovarian cancer is a relatively rare cancer with expert knowledge residing mainly at medical teaching centres, Ovarian Cancer Canada's (OCC) mission involves raising awareness of the disease. Specifically, OCC administers and sponsors a number of initiatives to encourage appropriate referral for suspicious ovarian masses and familial predisposition for ovarian cancer.

OCC sponsors online and face-to-face continuing medical education programs to educate family doctors regarding detection and management of ovarian cancer. These courses were developed by Memorial University's department of professional development in consultation with family physicians, the Society of Gynecologic Oncology of Canada and the Society of Obstetricians and Gynecologists of Canada. The online model is not facilitated, asynchronous and has an ask-the-expert feature with the opportunity to reflect and discuss via a discussion board (accreditation pending).

The face-to-face model has been adopted in a number of medical schools across the country in conjunction with annual family medicine workshops. Recently, the University of British Columbia department of continuing medical education adapted this program for rural physician education in a train-the-trainer model.

OCC also sponsors the Survivors Teaching Students program, which brings trained volunteers into the classrooms of medical schools to raise awareness of the disease. Key areas of focus are common misconceptions about ovarian cancer relating to identifiable symptoms, detection by Pap tests and HPV immunization as protection against it. This program is also available to nursing and pharmacy trainees.

As well, OCC distributes a factsheet for health professionals in primary care settings through mailings, continuing medical education courses and exhibits at medical conferences (http://www.ovariancanada.org/OCC-PDFs/OCC_HlthProFactSht_HiRezEN).

OCC also prepares fact sheets for women about:

- Signs and symptoms of the disease;
- Action to take in the presence of symptoms;
- The CA 125 test; and
- Risk factors.

Finally, OCC trains volunteers to conduct a one-hour education program, Knowledge is Power, for delivery at the community level that addresses ovarian cancer's signs, symptoms, risks and preventative factors.

Knowledge Gaps and Future Developments

Knowledge Gaps

The major knowledge gaps in ovarian cancer stem from our incomplete understanding of the disease's natural history.

At this time, there is no accepted precursor lesion for epithelial ovarian cancer, the most common type of ovarian cancer discussed in this paper. As well, there is debate surrounding both the tissue of origin and its pathogenesis.

Epithelial ovarian cancer is, as we have noted above, a heterogeneous group of diseases. Its subtypes have different morphologic appearances and underlying mutations; they behave differently clinically and respond differently to treatment.[19-22] Historically, this diverse group of cancers has been studied together because of the low incidence of each individual subtype and because they were all treated in the same way.

However, it now seems likely these subtypes may have different causal pathways. For example, endometrioid and clear-cell carcinomas appear to arise from endometriosis on the ovary.[23-25] Since ovarian carcinoma subtypes are immunophenotypically distinct, it is unlikely that a serum-screening assay for protein-based biomarkers will work for multiple subtypes. In future, understanding the pathogenesis of the different subtypes may lead to new histology-based screening and treatment approaches.

Serous adenocarcinoma is the most common histologic subtype of epithelial ovarian cancer.[26] No accepted precursor lesion has been identified in the ovary, despite attempts to describe such a lesion from the ovaries of women found to have early serous ovarian cancer at the time of a salpingo-oophorectomy.[27] Our lack of understanding of the changes leading to this malignancy means screening efforts are currently limited to identifying invasive disease in early stages, rather than preventing malignancy from occurring.

Recently, our assumptions regarding the initial development of serous adenocarcinoma of the ovary have been called into question. In the past, it was commonly accepted that this disease started de novo from epithelial cells lining the surface or inner inclusion cysts of the ovary.[28] Now, there are two main theories for the pathogenesis of malignant transformation of the ovarian surface epithelium.

The theory of incessant ovulation postulated that each ovulation event damages the surface epithelium and mutations are acquired during repetitions of the damage-repair process. These mutations accumulate to the point where cell growth and behaviour is not regulated, and cancer develops.[29]

The second theory postulated that gonadotrophins stimulate the ovarian epithelium directly, leading to accumulation of mutations that produce malignant transformation. This theory would explain why ovarian cancer is more common in the post-menopausal population where gonadotrophin levels are highest.[30] Population studies on risk factors for ovarian cancer support the hypothesis that it originates in the ovary's epithelium, with increased risk in women who have early menarche, late menopause, infertility, or low parity resulting in more ovulation events and hormonal stimulation over a lifetime.[31-33] Unfortunately, this hypothesis does not explain how the normal cells of the surface epithelium change their histologic appearance to resemble serous epithelium.

Recently, attention has been focused on the fallopian tube as a possible source of what we now call serous ovarian cancer. The fallopian tubes are normally lined with serous epithelium, and fallopian tube cancer is usually of serous histology.[34] Currently, cancer of the fallopian tubes is very rare, but this may be due to strict rules governing its pathologic diagnosis. For example, if there is tumour in both a fallopian tube and ovary, but there is more disease in the ovary than in the tube, the diagnosis by convention is ovarian cancer.[35,36]

Serous carcinomas of the ovary and tube behave similarly with peritoneal seeding of malignant cells being the predominant method of metastasis.[37] Since these cancers generally present in advanced stages at diagnosis with involvement of ovaries, tubes and peritoneal surfaces, it is difficult to determine the tissue of origin.[38] However, tubal intraepithelial carcinoma is generally accepted as a precursor lesion to invasive serous fallopian tube cancer.[11]

Meanwhile, early fallopian tube cancers and tubal intraepithelial carcinoma have been found with surprising frequency[39] in women genetically predisposed to ovarian cancer who undergo prophylactic salpingo-oophorectomies. These connections have led some researchers to hypothesize that the high-grade serous cancers of the ovary actually originate in the fallopian tube.[11,40-43] In this hypothesis, serous ovarian cancers are usually diagnosed at an advanced stage because once the cancer has spread from the fallopian tube to the ovary it has also likely spread to other locations. Perhaps our focus on early identification of ovarian cancer should be shifted to early identification of fallopian tube cancer and the identification of pre-malignant lesions, including tubal intraepithelial carcinoma.

This review highlights some of the important gaps in our current understanding of the natural history of epithelial ovarian cancer. Further research into alternative biomarkers such as serum-based DNA assays should be considered. Without truly understanding the underlying changes that lead to this disease, it is difficult to design tests to identify these changes early enough to decrease mortality. Better understanding of the disease origin and pathogenesis, including fallopian tube precursor lesions and in-situ carcinoma, should be an important focus of future research.

Future Developments

As outlined in the previous sections, current screening methods fail both to detect ovarian cancer at an early stage and to reduce disease-associated mortality. As high-grade serous carcinoma is responsible for the most deaths from ovarian cancer, the design of future screening assays should focus on this histological subtype to achieve the biggest impact.

Since carriers of BRCA1 and 2 genes are at a greater risk of developing high-grade serous carcinoma, they would be a suitable population to study this disease and potential early markers. Indeed, recent reports of unsuspected early-stage serous cancers (including intraepithelial carcinomas) discovered in the distal fallopian tubes of BRCA1 and 2 mutation carriers undergoing a prophylactic salpingo-oophorectomy provide a long-awaited promising lesion for identifying markers that may enable detection of early-stage serous carcinoma.[9-11,41,44] It is important to appreciate, however, that detection of these small tumours will require the use of exceedingly sensitive assays. A recent analysis by Brown et al suggests that serous cancers measure less than one centimetre in diameter during the "window of opportunity" for early detection; i.e., the period during which they are histologically detectable yet clinically occult.[45] Furthermore, the authors estimate that an annual screen (in both the high-risk and normal-risk population) would need to be capable of detecting a lesion 0.4 centimetres in diameter in order to achieve a 50 per cent reduction in the five-year serous carcinoma mortality rate.[45]

In addition to improving the detection of lethal serous carcinomas at an earlier stage, the development of molecular tests aimed at detecting markers of enhanced risk could greatly impact ovarian cancer mortality in two ways. First, if high-grade serous carcinomas progress as rapidly as is currently thought, the detection of molecular alterations prior to the initiation of malignancy would alert a health-care team to increase the testing intervals to ensure a window of opportunity for detecting early-stage cancer is not missed.

Second, characterization of these molecular alterations could contribute to the development of novel prevention strategies. These predictive markers could include molecular alterations found in histologically normal cells obtained from women known to be at an increased risk (most notably BRCA1 and 2 mutation carriers). The markers could also include molecular alterations characterizing each step of the recently proposed continuum of pre-cancer lesions in the distal fallopian tube.[10] Because not all of these lesions would be expected to progress to clinically apparent advanced-stage serous cancers,[45-47] we will need to

understand which molecular alterations drive the transition from one step to the next to minimize over-diagnosis and its associated negative impact on quality of life.

Finally, it is important to stress that molecular profiling studies aimed at identifying screening markers for detection of early cancer or increased risk cannot be based upon our previous approach of simply comparing normal to advanced cancer cells. A greater understanding of the natural history of serous carcinoma and other histotypes, including the cell type of origin and the factors contributing to each step of the progression from pre-malignancy to advanced cancer, have to be achieved before we can find meaningful screening markers that will greatly impact mortality.

Appendix 1: Requirements of an Effective Screening Test

For a screening test to be effective, it has to have efficacy, be acceptable to the target group and be valid.

Efficacy

Reduction in cancer mortality is the definitive requirement to confirm that a screening test is efficacious. Various intermediate indicators are useful as part of this process, including participation rates of the target group, cancer detection rates, interval cancer rates, and identifying the proportion of diagnosed cancers detected as a result of screening. If all are on target, eventually a reduction in cancer incidence (if anticipated) and mortality should be seen.

The desired outcome of screening for cancer is reduction in mortality from the disease with the population as the denominator (i.e., a screened population would experience a lower mortality rate from the cancer than an unscreened population). This reduction in mortality from the disease is not the same as reduction in case fatality (improvement in survival). Improved survival is expected for screening (because of lead time, length bias [often], selection bias and some degree of over-diagnosis) even if mortality is not reduced.

A screening test that identifies a cancer precursor will also result in reduction in cancer incidence, such as is seen for screening for cancer of the cervix and for colorectal cancer. Precursors of ovarian cancer have not been identified, so reduction in incidence is not anticipated as a result of screening.

However, simple case detection is not equivalent to efficacy as the cancer:

- may not be curable, nor have its natural history modified by available treatment; and
- may never have become life threatening in the patient's lifetime.

A screening test should not be offered to a population without efficacy first being demonstrated.

Acceptability

In screening programs, individuals who have not been diagnosed with the disease (for which the screening is offered) are approached to participate in the study. In general, that means they are healthy individuals, though it is possible to screen those already suffering from another condition. In practice, some individuals approached will have symptoms of the disease being screened for, but they or their medical adviser may not have recognized that disease is present.

In order to secure high compliance of the target group with the recommended screening schedule, the test should not involve too much embarrassment. Privacy and cultural beliefs must be respected. Those who accept screening should be inconvenienced as little as possible by the process needed to obtain the test, by the test itself and by its consequences. It helps considerably if the administration of the test is simple.

In general, screening tests that involve inspection and palpation are acceptable as well as tests that involve blood, saliva or urine collection. Also acceptable are X-rays and other forms of imaging.

Tests that involve the manipulation of feces or other body excreta are not so acceptable, nor are tests that involve endoscopy as well as rectal or vaginal examination. Acceptability is diminished if preparation for the test is complicated, such as is required for endoscopy. Tests that result in discomfort, especially if compression is involved, as for mammography, are less acceptable than, for example, a screening clinical breast examination.

Validity

The two components of validity of a screening test are sensitivity and specificity. These are two completely independent parameters, though in many circumstances there is a reciprocal relationship. Sensitivity is the proportion of individuals who have the disease and test positive. Specificity is the proportion of individuals free of the disease who test negative. A test with high sensitivity tends to have low specificity, and vice versa. These definitions are represented below:

Test result	Disease present	Disease absent
Positive	True positive (TP)	true negative (TN)
Negative	False negative (FN)	True negative (TN)

Sensitivity = TP/TP + FN
Specificity = TN/TN + FP

There are two process measures that are useful in terms of the yield of screening tests. The positive predictive value of a test, represented by TP/TP+FP, indicates the likelihood that an abnormal test will yield a finding of a cancer. The second useful measure is the negative predictive value, represented by TN/TN+FN, which reflects the proportion of normal screening tests that are truly normal.

The process of screening requires that individuals with a positive result undergo diagnostic tests to distinguish the true from the false positives. However, a corresponding evaluation does not occur for those who test negative, so that the false negatives are not identified. Thus, without special investigation, the true sensitivity of a test is unknown.[48]

In general, determination of sensitivity requires follow-up of those screened and identifying those who develop disease in the interval between screening tests. Then, sensitivity is represented by the expected incidence in the group screened less the interval cancer rate as a proportion of the expected incidence; i.e., the amount of disease destined to occur that did not occur because of the prior screen. The most valid way of determining sensitivity by this method is from randomized screening trial data, as the control (unscreened) group provides the measure of expected incidence of cancer in the population being studied.

Glossary

The Canadian Cancer Society website at www.cancer.ca and the National Cancer Institute website at www.cancer.gov were consulted for these definitions. Refer to these sites for more extensive listings.

Abnormal: Not normal. When it refers to a tumour, the tumour may be cancerous or likely to become cancerous.

Asymptomatic: Having no signs or symptoms of disease.

Benign: Not cancerous. Does not invade nearby tissue or spread to other parts of the body.

Bilateral salpingo-oophorectomy (BSO): A surgical procedure in which the ovaries and fallopian tubes are removed.

BRCA1 or BRCA2: Two genes that normally help to suppress the growth of tumours. A person who inherits an altered version (or mutation) of either the BRCA1 or BRCA2 gene has a higher risk of getting breast, ovarian, fallopian tube or prostate cancer.

CA 125: Cancer antigen 125 or carbohydrate antigen 125 is a protein that in humans is encoded by the mucin 16 (MUC16) gene. CA 125 has found its application as a tumour marker that, when elevated in some patients' blood, suggests the presence of some type of cancer.

Epithelial ovarian cancer: Cancer that occurs in the cells that line the ovaries.

Familial: An inherited disorder or trait that is present in some family members.

Gene: The basic biological unit of heredity that transfers traits from cell to cell and from parents to a child.

Gene mutation: A change or alteration in a gene that prevents it from working in the usual way.

Genetic testing: Scientific methods used to find out whether some people have a gene mutation that may result in having a greater chance of developing certain types of cancer.

Germ cell tumour: Cancer cells that arise from the ovaries' germ cells.

Grade: The grade of a tumour depends on how abnormal the cancer cells look under a microscope and how quickly the tumour is likely to grow and spread.

Hereditary: The process by which particular traits or conditions are passed from parent to child.

Hormone: A chemical substance that regulates body functions such as growth and reproduction.

Hysterectomy: Surgical removal of the uterus. The ovaries may also be removed at the same time (oophorectomy).

Mutate: To change the genetic material of a cell.

Oophorectomy: The surgical removal of one or both ovaries.

Salpingo-oophorectomy: The surgical removal of the fallopian tube(s) and ovary(ies).

Staging: The extent of a cancer within the body. It indicates to what extent the disease may have spread from the primary site to other parts of the body.

Stromal tumour: A tumour that begins in the tissues that support the ovary.

Total hysterectomy: Surgery to remove the uterus and cervix. The ovaries may also be removed at the same time (oophorectomy).

Transvaginal ultrasound (TVU): A procedure using sound waves to examine the vagina, uterus, fallopian tubes and bladder. An instrument is inserted into the vagina. A computer creates a picture called a sonogram using the echo of the sound waves.

References

[1] Canadian Cancer Society's Steering Committee. Canadian Cancer Statistics 2010. Toronto: Canadian Cancer Society; 2010.

[2] Karst AM and Drapkin R. Ovarian cancer pathogenesis: a model in evolution. J Oncol. 2010; 932371.

[3] Bast RC, Hennessy B, Mills GB. The biology of ovarian cancer: new opportunities for translation. Nat Rev Cancer. 2009 Jun;9(6):415-28.

[4] Yemelyanova AV, Cosin JA, Bidus MA, Boice CR, Seidman JD. Pathology of stage I versus stage III ovarian carcinoma with implications for pathogenesis and screening. Int J Gynecol Cancer. 2008 May-Jun;18(3):465-9.

[5] Soslow RA. Histologic subtypes of ovarian cancer: an overview. Int J Gynecol Path. 2008 Apr;227(2):161-74.

[6] Hogg R, Friedlander M. Biology of epithelial ovarian cancer: implications for screening women at high genetic risk. J Clin Oncol. 2004 Apr;22(7):1315-27.

[7] Shih IM, Kurman RJ. Ovarian tumourigenesis: a proposed model based on morphological and molecular genetic analysis. Am J Pathol. 2004 May;164(5):1511-18.

[8] Rossing MA, Wicklund KG, Cushing-Haugen KL, Weiss NS. Predictive value of symptoms for early detection of ovarian cancer. J Natl Cancer Inst. 2010 Feb 24;102(4):222-9.

[9] 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 Jan;100(1):58-64.

[10] Crum CP, Drapkin R, Miron A, Ince TA, Muto M, Kindelberger DW, Lee Y. The distal fallopian tube: a new model for pelvic serous carcinogenesis. Curr Opin Obstet Gynecol. 2007 Feb;19(1):3-9.

[11] Kindelberger DW, Lee Y, Miron A, Hirsch MS, Feltmate C, Medeiros F, Callahan MJ, Garner EO, Gordon RW, Birch C, Berkowitz RS, Muto MG, Crum CP. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. Am J Surg Pathol. 2007 Feb;31(2):161-9.

[12] Olivier RI, Lubsen-Brandsma MAC, Verhoef S, van Beurden M. CA125 and transvaginal ultrasound monitoring in high-risk women cannot prevent the diagnosis of advanced ovarian cancer. Gynecol Oncol. 2006 Jan;100(1):20-6.

[13] Berek JS, Hacker NF. Practical gynecologic oncology. Philadelphia: Lippincott Williams & Wilkins; 2000.

[14] Kobayashi H, Yamada Y, Sado T, Sakata M, Yoshida S, Kawaguchi R, Kanayama S, Shigetomi H, Haruta S, Tsuji Y, Ueda S, Kitanaka T. A randomized study of screening for ovarian cancer: a multicenter study in Japan. Int J Gynecol Cancer. 2008 May-Jun;18(3):414-20.

[15] Buys SS, Partridge E, Greene MH, Prorok PC, Reding D, Riley TL, Hartge P, Fagerstrom RM, Ragard LR, Chia D, Izmirlian G, Fouad M, Johnson CC, Gohagan JK. Ovarian cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: findings from the initial screen of a randomized trial. Am J Obstet Gynecol. 2005 Nov;193(5):1630-9.

[16] Partridge E, Kreimer AR, Greenlee RT, Williams C, Xu JL, Church TR, Kessel B, Johnson CC, Weissfeld JL, Isaacs C, Andriole GL, Ogden S, Ragard LR, Buys SS. Results from four rounds of ovarian cancer screening in a randomized trial. Obstet Gynecol. 2009 Apr;113(4):775-82.

[17] Menon U, Gentry-Maharaj A, Hallett R, Ryan A, Burnell M, Sharma A, Lewis S, Davies S, Philpott S, Lopes A, Godfrey K, Oram D, Herod J, Williamson K, Seif MW, Scott I, Mould T, Woolas R, Murdoch J, Dobbs S, Amso NN, Leeson S, Cruickshank D, McGuire A, Campbell S, Fallowfield L, Singh N, Dawnay A, Skates SJ, Parmar M, Jacobs I. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Lancet Oncol 2009 Apr;10:327-40.

[18] Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C et al for the PLCO Project Team. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA 2011 June 8;305(22):2295–303.

[19] Gilks CB. Subclassification of ovarian surface epithelial tumours based on correlation of histologic and molecular pathologic data. Int J Gynecol Pathol. 2004 Jul;23(3):200-5.

[20] Pieretti M, Hopenhayn-Rich C, Khattar NH, Cao Y, Huang B, Tucker TC. Heterogeneity of ovarian cancer: relationships among histological group, stage of disease, tumour markers, patient characteristics, and survival. Cancer Invest. 2002;20(1):11-23.

[21] Wang V, Li C, Lin M, Welch W, Bell D, Wong YF, Berkowitz R, Mok SC, Bandera CA. Ovarian cancer is a heterogeneous disease. Cancer Genet Cytogenet. 2005 Sep;161(2):170-3

[22] Madore J, Ren F, Filali-Mouhim A, Sanchez L, Köbel M, Tonin PN, Huntsman D, Provencher DM, Mes-Masson AM. Characterization of the molecular differences between ovarian endometrioid carcinoma and ovarian serous carcinoma. J Pathol. 2010 Feb;220(3):392-400.

[23] Campbell I, Morland S, Hitchcock A. Endometriosis and the relationship with ovarian cancer. In: Sharp F, Blackett T, Derek J, Bast R, editors. Ovarian Cancer 5. Oxford: ISIS Medical Media; 1998. p. 159-70.

[24] Bell K, Kurman R. A clinicopathologic analysis of atypical proliferative (borderline) tumours and well-differentiated endometrioid adenocarcinomas of the ovary. Am J Surg Pathol. 2000 Nov;24(11):1465-79.

[25] Dinulescu DM, Ince TA, Quade BJ, Shafer SA, Crowley D, Jacks T. Role of K-ras and Pten in the development of mouse models of endometriosis and endometrioid ovarian cancer. Nat Med. 2005 Jan;11(1):63-70.

[26] Pecorelli S, Odicino F, Maisonneuve P, Creasman W, Shepherd J, Sideri M, Benedet J. Carcinoma of the ovary. J Epidemiol Biostat. 1998;3:75-102.

[27] Bell D, Scully R. Early de novo ovarian carcinoma. A study of fourteen cases. Cancer 1994 Apr 1;73(7):1859-64.

[28] Scully R. Pathology of ovarian cancer precursors. J Cell Biochem Suppl. 1995;23:208-18.

[29] Fathalla M. Incessant ovulation—a factor in ovarian neoplasia? Lancet 1971 Jul 17;2:163.

[30] Cramer DW, Welch WR. Determinants of ovarian cancer risk. II. Inferences regarding pathogenesis. J Natl Cancer Inst. 1983 Oct;71(4):717-21.

[31] Risch HA, Marrett LD, Howe GR. Parity, contraception, infertility, and the risk of epithelial ovarian cancer. Am J Epidemiol. 1994 Oct 1;140(7):585-97.

[32] Risch HA, Weiss NS, Lyon JL, Daling JR, Liff JM. Events of reproductive life and the incidence of epithelial ovarian cancer. Am J Epidemiol. 1983 Feb;117(2):128-39.

[33] Cramer DW, Hutchison GB, Welch WR, Scully RE, Ryan KJ. Determinants of ovarian cancer risk. I. Reproductive experiences and family history. J Natl Cancer Inst. 1983 Oct;71(4):711-6.

[34] Lauchlan SC. Metaplasias and neoplasias of the Müllerian epithelium. Histopathology. 1984 Jul;8:543-57.

[35] Benedet JL, Bender H, Jones H, Ngan HYS, Pecorelli S. FIGO staging classifications and clinical practice guidelines of gynecologic cancers. Int J Gynaecol Obstet. 2000 Aug;70(2):209-62.

[36] Tavassoli FA, Mooney E, Gersell DJ, McCluggage WG, Konishi I. Surface epithelial-stromal tumours. In: Tavassoli FA, Devilee P, editors. Tumours of the breast and female genital organs. Lyons: IARC; 2001. p. 117–45.

[37] Heintz AP, Odicino F, Maisonneuve P, Quinn MA, Benedet JL, Creasman WT, Ngan HY, Pecorelli S, Beller U. Carcinoma of the fallopian tube. FIGO 6th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet. 2006 Nov;95 Suppl 1:S145-60.

[38] Lee YMD, Medeiros FMD, Kindelberger DMD, 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 Jan;13(1):1-7.

[39] Colgan TJ. Challenges in the early diagnosis and staging of Fallopian-tube carcinomas associated with BRCA mutations. Int J Gynecol Pathol. 2003 Apr;22(2):109-20.

[40] Piek JMJ, Kenemans P, Verheijen RHM. Intraperitoneal serous adenocarcinoma: a critical appraisal of three hypotheses on its cause. Am J Obstet Gynecol. 2004 Sep;191(3):718-32.

[41] Medeiros FMD, Muto MGMD, Lee YMD, Elvin JA, Callahan MJ, Feltmate C, Garber JE, Cramer DW, Crum CP. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. Am J Surg Pathol. 2006 Feb;30(2):230-6.

[42] Lee Y, Miron A, Drapkin R, Nucci MR, Medeiros F, Saleemuddin A, Garber J, Birch C, Mou H, Gordon RW, Cramer DW, McKeon FD, Crum CP. A candidate precursor to serous carcinoma that originates in the distal fallopian tube. J Pathol. 2007 Jan;211(1):26-35.

[43] Carlson JW, Miron A, Jarboe EA, Parast MM, Hirsch MS, Lee Y, Muto MG, Kindelberger D, Crum CP. Serous tubal intraepithelial carcinoma: its potential role in primary peritoneal serous carcinoma and serous cancer prevention. J Clin Oncol. 2008 Sep 1;26(25):4160-5.

[44] 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 Oct;25(10):1283-9.

[45] Brown PO, Palmer C. The preclinical natural history of serous ovarian cancer: defining the target for early detection. PLoS Med. 2009 Jul;6(7):e1000114

[46] Folkins AK, Jarboe EA, Saleemuddin A, Lee Y, Callahan MJ, Drapkin R, Garber JE, Muto MG, Tworoger S, Crum CP. A candidate precursor to pelvic serous cancer (p53 signature) and its prevalence in ovaries and fallopian tubes from women with BRCA mutations. 2008 May;109(2):168-73.

[47] 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 Sep;22(9):1133-8.

[48] Hakama M, Auvinen A, Day NE, Miller AB. Sensitivity in cancer screening. J Med Screen. 2007;14(4):174-7.