

Preventive Strategies in Epithelial Ovarian Cancer

Gina M. Mantia-Smaldone and Nathalie Scholler
*Penn Ovarian Cancer Research Center
University of Pennsylvania, Philadelphia,
USA*

1. Introduction

Despite advances in surgery and chemotherapy, epithelial ovarian cancer (EOC) remains the most lethal gynecologic malignancy ¹. Due to lack of a specific prodromal symptomatology as well as effective screening strategies, the vast majority of EOC patients present with advanced stage disease will ultimately die from their disease ¹. Furthermore, while up to 80% of patients will respond to conventional primary platinum/taxane chemotherapy, greater than 60% will experience disease recurrence, and current reports indicate discouraging response rates of 20% in women with resistance to platinum-based chemotherapy ². Preventive strategies, including improvements in early detection of disease as well as in preventing disease recurrence, are, therefore, crucial to improving prognosis.

Ovarian cancer prevention can be defined by two main strategies: 1) early detection of cancer in at-risk patients and 2) prevention of recurrent disease in patients with an established diagnosis of cancer. Through the use of screening tools, such as serum biomarkers and medical imaging, early disease detection offers the promise of identifying cancer while still localized and potentially curable ³. Secondary preventive approaches aim to maintain patients without evidence of active disease and thereby extend their disease-free survival. Surveillance methods including serial biomarker measurements as well as therapeutic vaccinations have been examined for their impact on survival outcomes. Finally, risk stratification is critical to the success of any cancer prevention strategy; capitalizing on risk-reducing behaviors and intensive screening is most likely to improve individuals at greatest risk for disease-related morbidity and mortality.

Current research in the early detection of ovarian cancer largely focuses on biomarker discovery, using transcriptome analysis, proteomics, epigenomics, metabolomics and glycomics of differentially expressed molecules between women with disease and healthy controls. Biomarkers already approved by the FDA (i.e., CA125 and HE4) or those under investigation, including osteopontin, MUC1 and mesothelin, offer hope for women at risk for disease development, especially those with predisposing genetic mutations ⁴. As part of this effort, we have generated site-specific biotinylated recombinant antibodies secreted by yeast (Biobodies ⁵) to cost- and time-effectively generate antibodies for developing screening tools for large populations of women ⁶. In addition, biomarkers, especially tumor associated antigens, may also serve as targets for vaccination ⁷.

Immune-driven therapies are currently under investigation for the prevention of ovarian cancer recurrence⁸⁻¹². Therapeutic vaccinations, targeting molecules specific to an individual's disease through the use of whole tumor lysates and tumor-pulsed dendritic cells, are currently under investigation for women with recurrent disease; such immunotherapeutic strategies are an additional research interest in our group (NCT00683241, NCT01132014, NCT00603460)^{13, 14}. Preventive approaches targeting individuals at risk for ovarian cancer as well as those with advanced stage disease may significantly impact disease incidence and prognostic outcomes. In this chapter, we will discuss these current approaches in detail.

2. Challenges in ovarian cancer prevention

In 1968, the World Health Organization (WHO) established guidelines for disease screening, including that the screened condition should be an important health problem with available treatment¹⁵. Ovarian cancer arguably satisfies these principles as it ranks as one of the top ten most common cancers amongst women in the US with more than 21,000 diagnosed annually¹. Further, ovarian cancer is the fifth most common cause of cancer mortality and remains the most lethal gynecologic cancer¹. Platinum/taxane chemotherapy is available for women with this disease, and approximately 70-80% will respond to this regimen¹. However, more than 75% of women are diagnosed when disease has already spread from the ovary, and advanced stage disease at presentation carries an overall poor prognosis¹. Improved ovarian cancer screening methods are therefore needed to detect disease in its earliest stages when treatment is more effective, translating into improved overall five year survival rates ranging from 60% to 90%^{3, 16, 17}.

The prevention strategy applied in cervical cancer demonstrates that successful disease screening significantly diminishes disease-related morbidity and mortality. The understanding of the natural history of cervical cancer led to the introduction of screening cervical cytology via Papnicolaou smears and guidelines for the early detection of preneoplastic cervical lesions. Since the introduction of these strategies, the incidence of cervical cancer has declined by more than 75%¹⁸. Furthermore, vaccination against the oncogenic Human papillomavirus (HPV) will also aid in eliminating this disease.

However, preventive strategies in ovarian cancer, unlike those in cervical cancer, have been met with several challenges. First, compared to cervical cancer which ranks as the second most common gynecologic cancer worldwide, ovarian cancer has a low prevalence with 40 cases per year per 100,000 women over the age of 50 years; this mandates that an effective screening test for ovarian cancer has both a high sensitivity and specificity in order to significantly impact disease incidence¹⁹. Second, current screening methods for early detection of ovarian cancer, including routine physical examination, CA125 serum assessment, and transvaginal ultrasound, have high false-positive rates and low positive predictive values (**Table 1**)²⁰. In fact, for a positive predictive value (PPV) of 10%, an ovarian cancer screening test would require a sensitivity of at least 75% and a specificity of greater than 99%²². Further, current methods of screening have not resulted in a significant impact on disease morbidity or mortality²¹.

While it is known that persistent HPV infection is responsible for virtually all cervical cancer and its immediate precursors worldwide²³, the exact etiology for ovarian cancer remains largely debated. Precursors for ovarian cancer should be "morphologically recognizable lesions that are reproducible thereby permitting early clinical intervention"²⁴. It has been

generally accepted that ovarian cancer originates from the ovarian surface epithelium (OSE) or from postovulatory inclusion cysts, and one hypothesis is that incessant ovulation is the main pathogenic mechanism^{25,26}. Yet, recent evaluation of pathologic specimens has also suggested that a greater proportion of “ovarian” cancers may actually originate in the fimbriated end of the fallopian tube with metastasis to the ovary^{26,27}. Further, a dualistic classification system has been proposed in which ovarian cancers are divided into two groups: type I tumors which consist of low-grade neoplasms and type II tumor which are aggressive and progress rapidly²⁸. Precursor lesions, including borderline malignant tumors and endometriosis, have been identified for type I tumors and may serve to improve early detection of these ovarian tumors especially given their indolent nature; a slower transition time between early and later stage of disease may afford opportunities to detect disease when it is still localized to the ovary. However, type II tumors do not have well-characterized precursor lesions, which is perhaps due to their high level of genetic instability²⁴. Because the transition time between stage I and stage III is unknown, it is uncertain whether these tumors rapidly progress from an early stage to an advanced stage or whether these tumors develop as a result of a diffuse peritoneal process¹⁹. At this point in time and despite a large body of work, no consensus has been reached regarding ovarian cancer precursors, which contributes to the challenge of creating an effective preventive strategy for ovarian cancer.

Finally, screening can carry some significant disadvantages, including an increased cost to society for over-utilized medical resources as well as psychological stress/anxiety especially in cases of false positive screening resulting in unnecessary operative intervention for benign pathology. However, thanks to stratifying approaches based on reproducible risk factors enabling maximized efficiency and balanced cost-effectiveness, this last hurdle may be easier to overcome.

Method	Sensitivity	Specificity	PPV
Symptomatology	57-83% ^{31,75}	86.7-90% ^{31,75}	1% ³⁴
Bimanual Exam	28% ¹⁴⁵	93% ¹⁴⁵	64% ¹⁴⁵
Ultrasound	75-95% ^{54,56,58}	73-98.7% ^{54,56,58}	1-46% ^{54,58}
CA125	57% ⁶⁸	85-93% ⁶⁸	96-100% ⁶⁸

Table 1. Current Ovarian Cancer Screening Methods.

3. Available modalities in prevention of late stage ovarian cancers and of disease recurrence

The goal of preventive strategies is to reduce ovarian cancer-related morbidity and mortality. Disease screening aims to detect ovarian cancer while it is still confined to the ovary and the five-year survival rates are 80-90%¹, thus to prevent incurable, late stage disease. Disease surveillance following conventional adjuvant chemotherapy allows for early detection of recurrent ovarian cancer and therefore permits prevention of clinically apparent recurrence. Current screening modalities include symptom recognition, bimanual exam, serial CA125 levels and pelvic ultrasound, while disease surveillance typically relies on physical exam, CA125 levels and imaging.

3.1 Do symptoms correspond with the onset of disease or with recurrence?

Ovarian cancer is referred to as the “silent killer” due to non-specific symptoms which often go unrecognized until the disease has significantly spread. Although there is limited

data to support symptomatology as a sole screening modality for ovarian cancer, recognition of ovarian cancer symptoms by both patients and caregivers may help to identify individuals with early stage disease ²⁹ and in 2007 the Gynecologic Cancer Foundation, American Cancer Society and Society of Gynecologic Oncologists issued a consensus statement supporting the recognition of symptoms as a modality in the evaluation of ovarian cancer ³⁰.

Patient symptoms have been correlated with the onset of disease ³¹⁻³³. Symptoms commonly attributed to ovarian cancer include abdominal bloating, increased abdominal size and urinary symptoms ³². In a case-control study of women at risk for developing ovarian cancer symptoms, specifically pelvic/abdominal pain, urinary urgency/frequency, increased abdominal size/bloating and difficulty eating/early satiety, were significantly associated with ovarian cancer when they occurred more than 12 days per month for less than one year duration ³¹. Further, a symptom index was more sensitive in women with advanced stage disease (79.5% vs. 56.7% early stage disease) and more specific in women greater than 50 years of age (90% vs. 86.7% for women less than 50 years old). The authors also applied this symptom index to a sample of 1709 women at average risk and reported a positive screening rate of 2.6%.

In a large population-based study ³⁴, Rossing and colleagues reported a positive symptom index in 62.3% of women with early stage disease compared to 70.7% with late-stage disease and 5.1% of controls. While symptoms were more likely to occur in women with ovarian cancer, there only was a short interval (less than 5 months) from symptom onset to diagnosis. This suggests that the symptom index may not provide a critical help to diagnose early stage ovarian cancer. In addition, the PPV of the symptom index was approximately 1%; thus the use of a positive symptom index alone would only result in the diagnosis of ovarian cancer in 1 out of 100 women in the general population presenting with the same symptoms.

Further complicating this screening technique is the fact that symptom presentation and duration may be influenced by the histological subtype of ovarian cancer ³⁵. In a recent population-base study, women with serous histology (the major histologic subtype) were less likely to report symptoms, were more often diagnosed at advanced stage (compared to mucinous tumors) and had a shorter duration of symptoms compared to women with early stage disease. This study also further highlights the difficulty in diagnosing ovarian cancer at an early stage due to rapid progression of disease.

Finally, monitoring symptoms in women with established ovarian cancer has also been considered for early intervention for disease recurrence. However, in a recent systematic review ³⁶, approximately 67% of a patients identified with recurrent disease had no concurrent clinical symptoms. Other surveillance modalities, including clinical examination, biomarker determination and imaging, should therefore be used in conjunction with symptoms in order to diagnose recurrent ovarian cancer.

3.2 Can bimanual examination diagnose early stage ovarian cancer and/or recurrent disease?

Routine pelvic examination is a key component of annual gynecologic health assessment. Palpation of the uterus and ovaries by bimanual examination may allow for the earlier detection of ovarian cancer; exam findings may initiate further evaluation with ultrasound

and ultimately surgery, potentially detecting cancers before they become clinically evident. Further, a pelvic exam has little adverse consequences³⁷.

However, pelvic examination is generally recommended only for the evaluation of symptomatic patients and only in conjunction with ultrasonography³⁸. Routine pelvic exam is considered as being neither a sensitive nor a specific means for detecting ovarian cancer in asymptomatic women^{39, 40} and may thus result in unnecessary surgical intervention for benign ovarian lesions. Further supporting this view, bimanual examination, which was originally included in the screening protocol of asymptomatic, postmenopausal women in the Prostate, Lung, Colorectal and Ovarian Screening Trial of the National Cancer Institute (NCI), was eliminated as a screening modality from the trial as it became evident that it failed to detect the first onset of ovarian cancer⁴¹.

In contrast, pelvic examination is recommended for disease surveillance of ovarian cancer per the NCCN guidelines, as 26-50% of recurrences occur within the pelvis⁴². Physical examination is an inexpensive, safe and practical tool that can trigger further evaluation with other modalities, but it must be kept in mind that the detection rates of recurrent ovarian cancer vary widely^{43, 44} and physical examination may fail to detect common sites of recurrence, including the upper abdomen, the retroperitoneum and the thorax⁴⁵.

3.3 How effective is ultrasound in detecting early stage ovarian cancer?

Pelvic ultrasound has been utilized for predicting the likelihood of malignancy, especially in women with a known pelvic mass. Transvaginal ultrasound (TVUS) can detect changes in ovarian size and morphology and is superior to physical examination in evaluating ovarian size, especially in women who are postmenopausal, obese or who have an enlarged uterus⁴⁶. Primary screening studies with TVUS in both asymptomatic and symptomatic at-risk women have been successful in identifying early stage ovarian cancers⁴⁷⁻⁵⁰.

Ovarian volume is inversely related to age; thus an enlarged ovary in post-menopausal women can be a sign of an evolving ovarian cancer. Mean ovarian volume is significantly greater in premenopausal women compared to postmenopausal women⁵¹; the upper limit of normal ovarian volume is 20 cm³ and 10cm³ in premenopausal and postmenopausal women, respectively. Other ovarian characteristics, including complex or solid morphology, cyst papillations, septae and increased blood flow, have also been suggested as findings suspicious for malignancy^{52, 53}.

To decrease the number of false-positive results, morphology scoring indices have been introduced for ovarian cancer screening. Investigators at the University of Kentucky have developed a morphology scoring index based on ovarian volume, wall structure and septal structure as a means to improve the PPV of TVUS for ovarian cancer screening⁵⁴. In a multi-institutional sample of patients undergoing surgical intervention for ovarian tumors, this morphology index implemented during preoperative ultrasound evaluation, yielded a sensitivity of 89%, a specificity of 73%, and a positive predictive value of 46%⁵⁵.

The International Ovarian Tumor Analysis (IOTA) study has also provided a reproducible standardized methodology for the ultrasound evaluation of adnexal masses and has further identified features with increased risk of malignancy: the presence of an irregular solid tumor, the presence of papillary or solid components, the presence of ascites, an irregular multilocular solid tumor and the presence of pronounced blood flow⁵³. Prospective validation of these simple ultrasound rules in a sample of women with adnexal masses yielded a sensitivity of 95%, a specificity of 91%, positive likelihood ratio of 10.37 and negative likelihood ratio of 0.06

⁵⁶. This study has also demonstrated that although pattern recognition of ultrasound findings by an experienced examiner can not only reproducibly discriminate between benign and malignant adnexal masses, it is superior to serum CA125 ⁵⁷.

The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) is a randomized control trial evaluating the effect of screening on mortality ⁵⁸. Patients are randomized to screening with CA125 and transvaginal ultrasound or with transvaginal ultrasound alone. At the prevalence screen, the results were promising for transvaginal ultrasound, which yielded a sensitivity, specificity and PPV of 75.0%, 98.2%, and 2.8%, respectively, for primary invasive epithelial ovarian and tubal cancers ⁵⁸. The impact of ultrasound screening on mortality is still pending at this time.

Ultrasound has also been examined for its role in the detection of ovarian cancer recurrence ⁴⁵. While sensitivity ranges 45-85% and specificity ranges 60-100% ⁴⁵, ultrasound has user variability and limited visibility ⁵⁹. For this reason, CT scans are often employed in surveillance protocols ⁴² and are typically only performed when indicated by clinical findings. In summary, although it is not the imaging modality of choice for ovarian cancer surveillance, TVUS is a useful tool to prevent the discovery of late stage ovarian cancer in women who are at increased risk for developing ovarian cancer.

3.4 What role do biomarkers play in the screening of ovarian cancer and the detection of disease recurrence?

Biomarkers are substances which help to indicate the presence of a disease. Soluble biomarkers differentially expressed between individuals with disease and normal controls are convenient tools of disease detection. The perceived advantages of biomarkers compared to other disease screening modalities such as physical exam or ultrasound, include availability, reproducibility, objectivity (operator-independent) and cost-effectiveness. Biomarkers for early detection aim to identify ovarian cancer in individuals who are symptomatic (Phase II specimens) or who are asymptomatic before a clinical diagnosis is made (Phase III specimens). However, the identification of such biomarkers is challenging. Discovery methods often use patient samples with clinically diagnosed and advanced stage disease, thus making it necessary to extrapolate findings of advanced disease to early-stage disease, and biomarkers discovered in diagnostic samples may not be validated in prediagnostic samples ⁶⁰.

CA125 (or MUC16) glycoprotein is the most studied tumor marker, alone and/or in combination with other biomarkers, for ovarian cancer screening. Approximately 80% of ovarian cancer tumors are CA125 positive ⁶¹. Elevated serum CA125 levels (>35 units/mL) can be detected in asymptomatic women with ovarian cancer using a monoclonal antibody (OC 125) ⁶² and carry a specificity of 98.5% for postmenopausal women ⁶³. An elevation in CA125 levels, especially twice the upper limits of normal, can often occur 2 to 5 months prior the clinical detection of an ovarian cancer recurrence ⁴⁵, with sensitivity and specificity for recurrence detection ranging from 62-94% and 91-100% ^{45, 64-66}. Recent work has further shown that CA125 levels may begin to rise as early as 3 years prior to clinical diagnosis, but will likely only reach detectable levels in the final year before diagnosis ⁶⁷.

While CA125 is the most predictive marker of ovarian cancer ⁶⁷ and remains the single-best marker ⁶⁸, studies have generally indicated that CA125 serum testing performs poorly in the detection of early stage disease ⁶⁹. CA125 levels are only elevated in approximately 50% of stage I ovarian cancers ⁶². Further, false positive CA125 levels can occur in women with

benign conditions, including menstruation, appendicitis, benign ovarian cysts, endometriosis and pelvic inflammatory disease, as well as with other malignancies, including breast, lung, endometrial and pancreatic cancers ⁶¹. Thus, multimodal strategies, particularly the combination of CA125 with pelvic ultrasound, have been examined in order to improve sensitivity and PPV of ovarian cancer screening.

The combination of CA125 and ultrasound has been examined in several studies ⁷⁰. In a prospective pilot study, 144 women with an elevated risk of ovarian cancer, as defined by a Receiver Operating Characteristic (ROC) curve based on age and CA125, underwent TVUS ⁷¹. Sixteen women were recommended for surgery and 3 women were found to have primary invasive ovarian cancer, thus yielding a specificity of 99.8% and a PPV of 19%. This algorithm was subsequently incorporated into the United Kingdom Collaborative Trial of Ovarian Cancer Screening, which is a randomized controlled trial designed to assess the effect of screening on mortality ⁵⁸. Women are randomized to three arms: no treatment, CA125 with TVUS screening or TVUS alone screening. At the prevalence screen, CA125 combined with TVUS achieved sensitivity, specificity, and positive-predictive values of 89.5%, 99.8% and 35.1%, respectively ⁵⁸. The specificity was higher in this combined screening group compared to the TVUS alone group (89.4% vs. 75.0%), suggesting that this screening would result in lower rates of repeat testing and surgery. In an additional study, an elevated serum CA125 (≥ 35 units/mL) and preoperative ultrasound findings of solid or complex tumors yielded a PPV of 84.7%, a NPV of 92.4% and correctly identified 77.3% of patients with early stage disease ⁷⁰.

Additional potential serum biomarkers have been identified ⁷²⁻⁷⁴ and extensively examined for the detection of ovarian cancer ⁷⁵⁻⁷⁷. Human epididymis protein 4 (HE4) is a biomarker overexpressed by both serous and endometrioid ovarian cancers ⁷⁸ and is expressed by 32% of ovarian cancers lacking CA125 expression ⁷⁶. HE4 has been FDA approved to monitor for disease recurrence (June 2008) and was recently incorporated into the clinical evaluation of ovarian cancer patients. Studies have also indicated that HE4 may also improve prediction of malignancy in ovarian masses when combined with CA125 measurements ⁷⁵⁻⁷⁶. Furthermore, Anderson and colleagues have demonstrated an increase in CA125, HE4 and mesothelin in ovarian cancer patients compared to matched controls, with a differential expression noted as early as 3 years preceding diagnosis; these results suggest that a multimarker profile may improve detection of early stage disease ⁶⁷.

Several panels of biomarkers have been published during the past ten years. One of them, a multiplex, bead-based, immunoassay system, examined serum concentrations of leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitory factor and CA125. This blood test, called OvaSure™, was reported to achieve a sensitivity of 95.3% and specificity of 99.4%, providing a significant improvement over CA125 alone for ovarian cancer detection in a cohort of women newly diagnosed with ovarian cancer compared to healthy controls ⁷⁹. OvaSure™ was proposed as a screening tool for women at risk for ovarian cancer, but, due to some concerns ⁸⁰, further investigation is warranted prior to the commercial use of this biomarker panel as a screening tool for the early detection of ovarian cancer.

The use of CA125 for detection of relapsed disease is not supported by the recent results of a randomized control trial ⁸¹. This multi-institutional European randomized control trial failed to demonstrate a survival advantage for women with recurrent disease who received early intervention based on rising CA125 levels compared to those who received treatment when symptoms developed ⁸¹. The authors thus questioned the value of routine CA125

measurements for surveillance of women with ovarian cancer who attain a complete response after first line therapy. Yet, the conclusions of this study have been underplayed by several concerns, including failure to address the role of secondary cytoreduction, lack of stratification by residual disease following primary cytoreduction, lack of radiographic confirmation of recurrence and non-standardized second-line therapies. Thus, the prevention of clinically detectable relapses using serial CA125 measurements will likely continue at the discretion of the patient and her physician⁸².

4. Biomarker discovery for ovarian cancer prevention

Various techniques are currently under investigation in order to identify new biomarkers which may improve the detection of early stage ovarian cancer as well as improve the detection of recurrent disease⁸³⁻⁸⁷. Proteomic analysis of serum and ascites samples by mass spectrometry is a strategy under investigation for the detection of differentially expressed proteins or protein fragments in women with ovarian cancer compared to healthy controls^{83, 88, 89}. Biomarkers and respective panels identified with proteomics have the potential to influence ovarian cancer prevention; further development and validation, however, are necessary before they may be introduced into clinical practice⁸⁹.

Evolving technologies, including transcriptomics⁸⁴, epigenomics^{85, 86}, metabolomics⁹⁰ and glycomics⁸⁷, are also under investigation in ovarian cancer. Transcriptomics, or expression profiling, studies the impact of RNA molecules, including mRNA, rRNA, tRNA and non-coding RNAs, in diseases. Using techniques based on DNA microarrays, these molecules can be identified to help pinpoint genes which may be differentially expressed in ovarian cancer compared to normal tissue⁸⁴. Gene expression profiling can be performed using both serum and formalin-fixed paraffin-embedded tissue biopsies and may help to identify genes associated with early-stage disease thereby improving screening⁸⁴.

Epigenomics focuses on the role of DNA methylation, histone modifications, RNA interference and nucleosome remodeling in the development and progression of ovarian cancer⁸⁶. Epigenetic alterations can be used as candidate targets for early detection and for monitoring of ovarian cancer recurrence⁸⁵. Aberrant DNA hypermethylation of CpG islands in the promoter of tumor suppressor genes and other cancer genes as well as microRNAs (miRNAs) are currently being identified in both body fluids and tissue biopsies and may help to demonstrate the importance of specific genes involved in ovarian tumorigenesis⁸⁵.

Metabolomics examines the role of small molecules (“metabolites”) which are unique to a specific cellular process. Metabolic fingerprints of ovarian cancer can be measured in serum and/or other bodily fluids using mass spectrometry and has the potential to improve detection of early stage and recurrent disease⁹⁰. Lysophosphatidic acid⁹¹ and lipid associated sialic acid⁹² are metabolites which are currently under investigation for ovarian cancer detection.

Glycosylation is the most common post-translational modification of proteins. Aberrant glycosylation patterns of proteins, such as MUC1⁹³, have been identified in ovarian cancer and may play a key role in promoting tumor cell invasion and metastasis as well as stimulating anti-tumor immune responses⁹⁴. Therefore, glycoproteins are currently being examined for their potential as biomarker as well as for treatment⁸⁷.

In addition to these efforts, we have generated a cost- and time-effective method for generating site-specific *in vivo* biotinylated recombinant antibodies secreted by yeast

(Biobodies ^{5, 95}). Biobodies have been generated against HE4 ⁹⁵ and mesothelin ⁹⁶. We have also demonstrated that this technology can be used reliably in a highly-sensitive bead-based ELISA assay for screening large populations of women for ovarian cancer ^{5, 67} and for serum biomarker discovery ⁶.

These novel approaches to biomarker discovery offers promise for improved ovarian cancer screening and for detection of recurrences. The impact of these biomarkers on clinical outcomes warrants further investigation in prospective clinical trials.

5. Current recommendations for ovarian cancer prevention

Given its low prevalence in the general population, universal screening for ovarian cancer is neither feasible nor cost-effective. Risk assessment is inherent to the success of any screening approach, and women at highest risk for disease are likely to benefit the most from preventive strategies. Several risk factors have been identified for epithelial ovarian cancer (**Table 2**) ²⁵, and current screening recommendations are often stratified by an individual's risk of developing disease. While the exact pathogenesis of this disease is still unclear, it is generally postulated that an increase in ovulation and/or an increase in estrogen exposure is associated with an increased lifetime risk of disease. Thus, factors, such as nulliparity, menarche at an early age, menopause at a late age, fertility drug use and hormone replacement therapy use, are believed to put individuals at risk for disease ^{25, 97-101}. Age, Caucasian race, ethnicity (especially Ashkenazi Jewish heritage), living in an industrialized country, and a history of endometriosis are other factors predisposing to ovarian cancer ²⁵. In addition, several factors, particularly multiparity, oral contraceptive use, breastfeeding and tubal ligation, have been linked with a decreased incidence of ovarian cancer and are therefore believed to be protective against developing ovarian cancer ^{102, 103}.

Protective Factors	Risk Factors
Hysterectomy	Age
Tubal Ligation	Caucasian race
Multiparity	Early menarche
Lactation	Ethnicity (Ashkenazi Jewish, Icelandic, Hungarian)
Oral Contraceptive use	Family history
	Fertility drug use
	Hormone replacement therapy
	Late menopause
	Nulliparity
	Personal history of breast cancer
	Residence in North America and Northern Europe
	Talc
	Endometriosis

Table 2. Protective and Risk factors for Ovarian Cancer ²⁵.

Perhaps, the single most important risk factor for ovarian cancer is family history. Hereditary ovarian cancers account for approximately 10% of all EOC cases. Compared to controls, women with one first or second-degree relative with ovarian cancer have a three-

fold increase in risk ¹⁰⁴. Hereditary ovarian cancers are commonly attributed to genetic mutations which are transmitted in families in an autosomal dominant fashion. Germline mutations in *BRCA1* and *BRCA2*, tumor suppressors which participate in homologous recombination repair of double-stranded DNA breaks, account for approximately 95% of all hereditary EOC cases ¹⁰⁵ and carry a 25 to 50% lifetime risk of ovarian cancer ¹⁰⁶. Further, *BRCA1/2* mutations are highly prevalent amongst women of Ashkenazi Jewish descent; 35-40% of Ashkenazi women with ovarian cancers have a *BRCA1* or *BRCA2* mutation ¹⁰⁷. These mutations may also be suspected in individuals with a personal history of breast cancer before age 50, dual breast cancer or ovarian cancer ¹⁰⁸. Women with *BRCA*- associated ovarian cancer typically present with high grade serous cancers at an earlier age compared to non-hereditary controls; however, these individuals more often have higher response rates to platinum-based chemotherapy and improved overall survival ¹⁰⁹.

The remaining hereditary EOC cases are attributed to Lynch Syndrome II, also referred to as hereditary nonpolyposis colorectal cancer (HNPCC) syndrome; these individuals with mutations in DNA mismatch repair genes *MLH1*, *MSH2*, *MSH6* and *PMS2* are at increased risk for colon cancer as well as numerous other cancers, including endometrial and ovarian cancer ¹¹⁰. Women with this autosomal dominant genetic background have a 3 to 14% lifetime risk of ovarian cancer ¹¹⁰.

5.1 Recommendations for ovarian cancer prevention in women at average risk

In the absence of significant risk factors, a typical woman carries a 1 in 72 lifetime risk of ovarian cancer ¹¹¹ and is considered at average risk of developing ovarian cancer.

5.1.1 Prevention by risk reducing behaviors

Epidemiologic studies of women with ovarian cancer risk have identified several protective factors, including oral contraceptive pill use (OCP), parity, lactation, and tubal ligation (**Table 2**). These protective factors should be considered for women with any risk of ovarian cancer as an additional preventive strategy. Patients should be counseled regarding the impact of these factors on their risk of ovarian cancer. Specifically, (1) the use of OCPs for 5 or more years results in a 50% reduction in the incidence of ovarian cancer ¹⁰², and this benefit may last for up to 30 years following use ¹¹². This benefit has also been reported in women with *BRCA1* or *BRCA2* mutations ¹¹³ and for most histological subtypes ¹¹⁴. It is estimated that OCPs have prevented 200,000 ovarian cancers and 100,000 deaths ²⁵. (2) Parity is a protective factor for ovarian cancer ²⁵. The risk for ovarian cancer decreases with each live birth, but there is no additional benefit once a woman achieves grand multiparity ¹¹⁵. Parous women with *BRCA1* mutations can also experience a reduced risk of ovarian cancer with each additional full-term pregnancy ¹¹⁶. (3) Lactation also results in a decreased incidence of ovarian cancer¹¹⁷. However, there is no additional benefit for individual episodes of lactation beyond 12 months. The relative risk of ovarian cancer decreases by 2% for each month of breastfeeding ¹¹⁸. (4) Tubal ligation may also substantially reduce the risk of ovarian cancer ¹¹⁹. Given a greater than 60% risk reduction, women with *BRCA1* mutations should be counseled regarding this option especially when they have completed childbearing ¹²⁰.

5.1.2 Prevention by routine screening

Given a low incidence and prevalence of ovarian cancer in the general population, large study cohorts are necessary to evaluate the utility of an ovarian cancer screening test ¹²¹. The

results of initial clinical trials, while failing to evaluate the impact of screening on cancer-related mortality, emphasize limitations on the specificity and PPV of available screening strategies for women at average risk.

A pilot randomized control trial evaluated a multimodal screening approach with serial CA125 and pelvic ultrasound in a sample of almost 22,000 postmenopausal women¹²¹. Combined CA125 and ultrasound (US) screening was not only feasible but also preliminarily resulted in a survival advantage (median survival 72.9 months in the screened group vs. 41.8 months in the control group, $p = 0.0112$). Data from this trial have paved the way for larger randomized-control trials^{21, 58, 122} which aim to examine the impact of screening on mortality.

The Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS) trial was a prospective, randomized trial examining ovarian screening, via CA125 and US, in asymptomatic postmenopausal Japanese women between 1985 and 1999¹²². Of more than 41,000 women who underwent screening, only 27 had detected ovarian cancer; at the prevalent screen, screening produced a detection rate of 0.31 per 1000. Ovarian cancer screening also identified a higher proportion of stage I cancers (63% vs. 38%, $p=0.23$) when compared to the control group.

The Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) screening trial is a randomized controlled cancer screening trial evaluating screening tests for the 4 PLCO cancers⁴¹. More than 78,000 healthy women between 55 and 74 years of age from across the United States were randomized to a screening or usual care arm at 10 screening sites between 1993 and 2001. The primary objective of this trial was to determine whether routine screening via transvaginal ultrasound (TVUS) and/or CA125 can reduce ovarian cancer-specific mortality. Twenty-nine neoplasms were identified in almost 29,000 women who received any screening test, producing a PPV for TVUS of 1.0%, 3.7% for CA125, and 23.5% for combined TVUS and CA125. Overall, these screening tests were associated with a high number of false-positive tests, especially for women who were younger, heavier, and had a history of prior hysterectomy¹²³. Further, TVUS and CA125 failed to produce a significant impact on ovarian cancer mortality, and 15% of women with false-positive screening experienced serious resulting complications²¹. The results of this trial suggest that routine screening with CA125 and TVUS should not be performed in asymptomatic women at low-risk for ovarian cancer.

The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) is a large randomized control trial evaluating TVUS and/or CA125 versus no screening in sample of more than 200,000 postmenopausal women between 2001 and 2005⁵⁸. The primary objective of this study is to determine whether screening affected ovarian cancer-related mortality. In the prevalence screen, 42 primary ovarian and 45 fallopian tube cancers were identified with 48.3% of these cancers reported as stage I or II disease. The sensitivity, specificity and PPV for primary invasive epithelial ovarian and tubal cancers were 89.5%, 99.8% and 35.1% for combined TVUS and CA125 versus 75.0%, 98.2%, and 2.8% for TVUS alone, respectively. Thus, combination screening methods yielded the lowest number of false-positive screens, translating into lower rates of repeat testing and surgery. While this initial screen indicates that these screening strategies are feasible, the impact of these tests on mortality is still pending at this time.

In summary, the latest studies suggest that risk reducing behaviors can provide significant prevention of ovarian cancer, while routine screening for ovarian cancer in women at

average risk does not improve the prevention of late-stage disease and is currently not recommended by any professional society ²⁵.

5.2 Recommendations for ovarian cancer prevention in women at increased risk

Women with a strong family history of either ovarian or breast cancer alone are considered to be at higher-than-average risk, while women with confirmed mutations in *BRCA1* or *BRCA2* and those with Lynch syndrome are at the highest risk of developing ovarian cancer. Genetic risk assessment should be performed in individuals to provide “individualized and quantified assessment of risk as well as options for tailored screening and prevention strategies” ¹⁰⁸. The Society of Gynecologic Oncologists recommends genetic screening in women with a 20-25% risk of having an inherited predisposition to breast and ovarian cancer: (1) women with a personal history of both breast and ovarian cancer (including those with primary peritoneal or fallopian tube cancers); (2) women with ovarian cancer and a close relative with breast cancer at ≤ 50 years or ovarian cancer at any age; (3) women with ovarian cancer at any age who are of Ashkenazi Jewish ancestry; (4) women with breast cancer at ≤ 50 years and a close relative with ovarian or male breast cancer at any age; (5) women of Ashkenazi Jewish ancestry and breast cancer at ≤ 40 years; or (6) women with a first or second degree relative with a known *BRCA1* or *BRCA2* mutation ¹⁰⁸. Further, risk assessment is recommended if women have a 20-25% of having an inherited predisposition to endometrial, colorectal and related cancers, including: those patients meeting the revised Amsterdam criteria ¹²⁴ and those with personal or family history concerning for Lynch Syndrome ¹⁰⁸.

5.2.1 Prevention by risk reducing behaviors and surgery

In addition to the risk reducing behaviors described earlier for women at average risk,, prophylactic surgery should be strongly considered in women at high risk for ovarian cancer. Risk-reducing salpingo-oophorectomy (RRSO) is associated with an 80% risk reduction in *BRCA1/2*-associated ovarian, fallopian tube or primary peritoneal cancer ^{125, 126}. Women with *BRCA* germline mutations have a significant survival advantage following risk-reducing surgery compared to disease surveillance ^{125, 126}. This approach has also been reported as a cost-effective strategy ^{127, 128}. Women with *BRCA1/2* germline mutations should be counseled on risk-reducing strategies, and RRSO should be recommended upon completion of childbearing or by age 40 ²⁵.

Risk-reducing hysterectomy and bilateral salpingo-oophorectomy is also a feasible preventive approach in women with Lynch Syndrome, with risk reduction approaching 100% ¹²⁹. Recent cost-effective analyses demonstrated that risk-reducing surgery is the most cost-effective gynecologic cancer prevention strategy in this patient population ^{128, 130}.

5.2.2 Prevention by routine screening

Current opinion suggests that screening may be appropriate for women in these increased risk categories. However, while intensive screening is recommended for women with *BRCA1* and 2 mutations, studies have indicated that screening with CA125 and TVUS are ineffective ^{131, 132} because the majority of cancers are still detected at advanced stages. In a retrospective study of 241 women with confirmed *BRCA1* or *BRCA2* mutations, surveillance with annual pelvic exam, transvaginal ultrasound and serum CA125 level failed to effectively identify women with early stage disease ¹³¹.

Currently, women with HNPCC/Lynch Syndrome are offered active disease surveillance including annual TVUS, endometrial biopsy and CA125 ¹⁰⁸. Auranen and colleagues performed a systematic review of the literature to determine the role of screening in women with HNPCC or with a family history of HNPCC ¹³³. Of five studies meeting inclusion criteria, only three examined the utility of CA125 surveillance for ovarian cancer in this patient population. In total, five ovarian cancer cases, none of which were reported as early stage disease, were detected by CA125 surveillance. Based on the current available published evidence, the authors concluded that there is no benefit for ovarian cancer screening in this patient population.

In summary, while studies have failed to demonstrate a benefit for screening in high risk patients, risk-reducing surgery is the most cost-effective gynecologic cancer prevention strategy and screening with serial CA125 levels and TVUS is generally recommended until risk-reducing surgery can be performed.

5.3 Recommendations for ovarian cancer prevention in women with pelvic masses

Several investigators have introduced risk models which would allow for the preoperative risk assessment of women with pelvic masses ¹³⁴⁻¹³⁷. The Risk of Malignancy Index (RMI) is a diagnostic model combining CA125 levels, imaging and menopausal status; at a cutoff level of 200, the RMI produced a sensitivity of 85% and a specificity of 97% and was an effective model for discriminating between cancer and benign lesions ¹³⁷. The Risk of Ovarian Malignancy Algorithm (ROMA) is another model which predicts the likelihood of ovarian cancer in women with pelvic masses by the combination of HE4 and CA125 serum levels with menopausal status ¹³⁶. This algorithm has shown promising diagnostic performance for the detection of ovarian cancer in postmenopausal women, with a sensitivity of 82.5% ¹³⁶, and has also been shown to perform better than the RMI model for risk prediction of ovarian cancer ^{134, 135}. This model may therefore be an effective strategy for triaging patients with pelvic masses.

5.4 Current recommendations for preventing disease recurrence

5.4.1 Role of disease surveillance

Active disease surveillance aims to detect recurrent ovarian cancer in asymptomatic women in order to provide opportunities for early intervention and ultimately improved outcomes. However, current surveillance recommendations are often based on expert opinions and practice patterns. The National Comprehensive Cancer Network (NCCN) recommends routine visits every 2 to 4 months for 2 years, then every 3 to 6 months for 3 years, followed by annual visits after 5 years ⁴². A physical examination, serum CA125 and laboratory and imaging (as clinically indicated) are to be performed at each visit.

In response to the MRC OV05/EORTC 55955 trial ⁸¹, the Society of Gynecologic Oncologists issued a statement on the use of CA125 for monitoring ovarian cancer in June 2009: "Although there may not presently be a major survival advantage to the use of CA125 monitoring for earlier diagnosis of recurrence, patients and their physicians should still have the opportunity to choose this approach as integral to a philosophy of active management" and that "patients and their physicians should be encouraged to actively discuss the pros and cons of CA125 monitoring and the implications for subsequent treatment and quality of life" ⁸².

A systematic review of the literature demonstrated that routine surveillance was able to detect 67% of asymptomatic recurrences with a lead time of 3 months but that published

studies failed to demonstrate a survival advantage of early detection of ovarian cancer by routine surveillance³⁶. The authors suggest that routine surveillance should be reconsidered in current practice.

5.5 Immunoprevention of disease recurrence

While 70-80% of patients with advanced EOC will initially respond to conventional platinum/taxane therapy, more than 60% will experience a recurrence of disease and 70-90% will ultimately die of their disease². Immune-driven vaccines are currently under investigation for the prevention of ovarian cancer recurrence⁸⁻¹².

Host anti-tumor immune responses have the potential to significantly influence prognosis in ovarian cancer patients. The presence of tumor-infiltrating lymphocytes (TILs) has been correlated with significantly improved progression-free and overall survival rates in women with advanced stage ovarian cancer compared to women without TILs^{138, 139}. Thus, given that ovarian cancer is intrinsically immunogenic, it may be possible to enhance host anti-tumor immune responses by using vaccines which strengthen TIL responses and thereby improve patient outcomes by preventing recurrent disease.

Therapeutic vaccinations derived from autologous whole tumor cell lysates may help to enhance host antigen-specific anti-tumoral immune responses¹⁴. The main advantages of these vaccines are "the opportunity to induce immunity to a personalized and broad range of antigens" and the incorporation of yet unidentified tumor antigens¹⁴⁰. A recent meta-analysis of 173 immunotherapy trials, including ovarian and other primary cancers, demonstrated a higher objective clinical response in individuals receiving whole tumor antigen-based vaccines compared to those receiving synthetic antigens (8.1% vs. 3.6%, respectively; $p < 0.001$)¹⁴¹. The Penn Ovarian Cancer Research Center is currently conducting a phase I/II randomized study to determine the feasibility, safety and immunogenicity of a vaccine derived from autologous oxidized tumor cell lysate (OC-L) in combination with Ampligen, a Toll-like receptor 3 agonist (NCT01312389).

Vaccination with antigen-specific dendritic cells (DCs) can enhance anti-tumor immunity via specific tumor-antigen presentation and activation of effector T cells¹⁴². There are several approaches to DC-based vaccines, including exposure of DCs to whole tumor cell lysates, defined ovarian tumor peptides, and ovarian tumor cells, to induce a cytotoxic T lymphocyte (CTL) response¹⁴³. In a phase I trial, three of six patients with progressive or recurrent ovarian cancer experienced stabilization of disease following administration of autologous tumor antigen-pulsed DCs with reported progression-free intervals of 8-45 months¹⁴⁴. Given these promising data, DC-based vaccines are currently the focus of several new trials (NCT00703105, NCT00683241, and NCT01132014) which will hopefully demonstrate an impact on long-term prognosis. The Penn Ovarian Cancer Research Center is currently examining the feasibility and immunogenicity of a DC vaccine loaded with autologous tumor lysate administered intranodally, alone or in combination with intravenous Bevacizumab (NCT01132014). A phase I/II trial is also underway at our institution in which patients with recurrent EOC or primary peritoneal cancer will undergo adoptive transfer of ex vivo CD3/CD28-costimulated autologous peripheral blood T cells along with tumor lysate-pulsed DC vaccination (DCVax®-L) (NCT00603460) in order to determine the feasibility and safety of this combination and progression-free survival at 6 months.

6. Conclusion

Ovarian cancer is the most lethal gynecologic cancer in the United States. Given the low prevalence of this disease in the general population, risk assessment is crucial to the success of available preventive strategies. However, current primary preventive strategies, even in women at high risk, have not proven reliable in the detection of early stage disease nor have they significantly impacted disease related mortality. Thus, risk-reducing behaviors and surgery should be considered in women at high risk for ovarian cancer.

In the near future, novel technologies may help to better characterize critical pathways in ovarian carcinogenesis and therefore result in biomarkers and/or multimarker panels more effective than CA125 alone, in both detecting early stage disease as well as recurrences. Validations of proposed strategies are under investigation in ongoing studies (**Table 3**).

Trial Name	Trial Identifier	Primary Investigator	Study Status	Study Population	Method(s) under investigation	Objective
Prospective Study of Risk-Reducing Salpingo-Oophorectomy and Longitudinal CA-125 Screening Among Women at Increased Genetic Risk of Ovarian Cancer ¹⁴⁶	NCT00049049	Green, M.H.	Closed	Increased genetic risk	Screening (TVUS, CA125, ROCA) vs. RR surgery (RRSO + screening)	Compare the prospective incidence of ovarian cancer, breast cancer, fallopian tube cancer, primary peritoneal cancer, and all cancer in participants at increased genetic risk of ovarian cancer who undergo risk-reducing salpingo-oophorectomy (RRSO) or screening
The UK Familial Ovarian Cancer Screening Study	NCT00033488	Mackay, J.	Closed to Accrual (as of 3/31/2010)	Increased risk due to strong family history	TVUS, CA125	Determine an optimal screening procedure for ovarian cancer, in terms of the most appropriate screening test, criteria for interpretation of results and screening intervals, in women at high genetic risk for developing ovarian cancer
Quality of Life Associated With a Low-Risk Screening Program for Ovarian Cancer	NCT00511641	Bodurka, D.C.	Currently Recruiting	Average risk, postmenopausal women	CA125	The goal of this research study is to learn more about how women feel about an ovarian cancer screening program that involves getting a blood test to measure CA 125 levels. This includes finding out about women's quality of life and whether they are concerned or worried about their risk of developing cancer. This study also seeks to find out whether elevated CA 125 levels affect participants in terms of cancer worries or concerns.

Trial Name	Trial Identifier	Primary Investigator	Study Status	Study Population	Method(s) under investigation	Objective
United Kingdom Collaborative Trial Of Ovarian Cancer Screening ^{58, 147}	NCT00058032	Menon, U.	Closed	Average risk, postmenopausal women	CA125, US	Randomized clinical trial to study the effectiveness of ultrasound with or without measuring CA 125 levels in detecting ovarian cancer in postmenopausal women.
Ovarian Cancer Screening Pilot Trial in High Risk Women	NCT00039559	Skates, S.J.	Active	At increased genetic risk	CA125, ROCA	Screening trial to determine the significance of CA 125 levels in detecting ovarian cancer in participants who have a high genetic risk of developing ovarian cancer
Northwestern Ovarian Cancer Early Detection & Prevention Program	NCT00005095	Shulman, L.P.	Active	At high risk due to family or personal medical history	Symptoms, biomarkers, CA125, physical exam, TVUS	This clinical trial is studying screening methods for identifying women who are at increased risk for developing ovarian cancer
Specialized Program Of Research Excellence (SPORE) In Ovarian Cancer/Cancer Genetics Collaborative Ovarian Cancer Screening Pilot Trial In High Risk Women	NCT00080639	Patridge, E.E.	Closed	At high risk due to family history, genetic mutation or ethnic background	CA125	This phase II trial is studying CA-125 levels in screening for cancer in women who are at high risk of developing ovarian cancer
A Randomized Controlled Trial Using Novel Markers to Predict Malignancy in Elevated-Risk Women ^{67, 75, 148}	NCT01121640	Urban, N. and Karlan, B.	Recruiting	At increased risk due to BRCA mutation, personal or family history or elevated biomarker screen	CA125, HE4, TVUS	The Novel Markers Trial will compare the safety, feasibility and effectiveness of two different epithelial ovarian cancer screening strategies that use CA125 and add HE4 as either a first or second line screen. This study is the next step in a larger research effort to develop a blood test that can be used as a screening method for the early detection of epithelial ovarian cancer.
Cancer Screening and Prevention Program for High Risk Women	NCT00849199	Muggia, F.	Recruiting	At increased risk due to personal or family history or who are perceived at increased risk	Questionnaire, pelvic exam, Pap smear, mammogram, TVUS, CA125	The purpose of this study is to evaluate screening and prevention in women with high risk of ovarian or breast cancer.

Trial Name	Trial Identifier	Primary Investigator	Study Status	Study Population	Method(s) under investigation	Objective
Efficacy of a Combined Program for Early Detection of Breast and Gynecological Cancers in Low Resource Countries ^{31, 32, 49, 58}	NCT01178736	Yang W, Singh D, and Filho A.	Not Yet Recruiting	Symptomatic postmenopausal women age 50-64	TVUS, PE	The purpose of this study is to implement a community-based combined program for early detection of breast, cervical, ovarian and endometrial cancer in low-resource countries delivered through a free standing or a mobile Well Woman Clinic
Screening and Identification of Novel Diagnostic and Prognostic Biomarkers on Ovarian Cancers	NCT00854399	Cheng, W.F.	Recruiting	Women with documented ovarian cancer	mesothelin	To further evaluate the role of mesothelin in ovarian cancer and elucidate the potential of mesothelin as a target antigen for immunotherapy.
Ovarian Cancer Early Detection Screening Program	NCT01292733	Paley, P.	Recruiting	At increased risk due to family history, Ashkenazi Jewish ethnicity, male relative with breast cancer or high likelihood of BRCA mutation	CA125, TVUS, Health Status Questionnaire	The main purpose of this program is to see whether periodically measuring CA-125 (tumor marker) levels in the blood and undergoing transvaginal ultrasounds over time will be effective in the early detection of ovarian cancer
Development of an Assay for the Early Detection of Ovarian Cancer	NCT00986206	Brard, L.	Recruiting	Pelvic Mass, diagnosed EOC or known BRCA carrier	Lyso phosphatidic acid (LPA)	This clinical trial is studying using the lysophosphatidic acid assay to see how well it works in early detection of ovarian cancer in patients with ovarian cancer or who are at risk for ovarian cancer.
The University of Louisville Ovarian Screening Study	NCT00267072	Helm, C.W.	Completed	Asymptomatic Postmenopausal women or premenopausal women at risk due to personal or family history, BRCA mutation, or prior fertility drug use	Tumor membrane fragments	The objectives of this study are: To identify women at increased risk for developing ovarian cancer To detect ovarian cancers at an early stage To investigate the role of tumor membrane fragments as tumor markers for early ovarian carcinoma

Trial Name	Trial Identifier	Primary Investigator	Study Status	Study Population	Method(s) under investigation	Objective
Assessment of Screening Modalities for Gynecologic Cancers	NCT00879840	Sherman, M.E.	Recruiting	Postmenopausal women with confirmed or suspected ovarian cancer who will be having surgery	Assess alternative tissue sampling techniques; DNA methylation pattern	DNA will be extracted from samples collected using a vaginal Tampon and an endometrial brushing using an FDA approved device (Tao brush) prior to surgery. A panel of methylation markers will be analyzed from samples yielding sufficient DNA. The results of the methylation analysis will be compared to the final histology for all patients in the study.
NYU Ovarian Cancer Early Detection Program Blood and Genetics	NCT00531778	Pothuri, B.	Terminated	At increased risk due to personal or family history of breast and/or ovarian cancer or due to genetic mutations in BRCA or mismatch repair genes (i.e., Lynch syndrome), or fertility drug use	molecular, biochemical, functional, and genetic markers	To identify and develop highly sensitive and specific tumor markers that can be applied to population-based screening for the early detection of ovarian cancer.
PROTOCOL FOR THE NCI PROSTATE, LUNG, COLORECTAL, AND OVARIAN (PLCO) CANCER SCREENING TRIAL ^{41, 123, 149, 150}	NCT00002540	Berg, C.	Ongoing, Closed to recruitment	Average risk, postmenopausal women	CA125, TVUS	Determine whether screening with CA 125 and transvaginal ultrasound can reduce mortality from ovarian cancer in women aged 55-74
Use of the CA 125 Algorithm for the Early Detection of Ovarian Cancer in Low Risk Women	NCT00539162	Lu, K.	Recruiting	Average risk, postmenopausal women	CA125	To evaluate the longitudinal CA-125 algorithm for the early detection of ovarian cancer in a low risk cohort of women

Trial Name	Trial Identifier	Primary Investigator	Study Status	Study Population	Method(s) under investigation	Objective
A Pilot Study of Short Non-coding RNA Biomarkers of Predisposition to Ovarian Cancer	NCT01187602	Jazaeri, A.	Recruiting	Women at average risk, increased risk and with ovarian cancer	sncRNA	The purpose of this study is to create new tests to identify biomarkers for ovarian cancer so that a screening test can be developed. For patients who have a diagnosis of ovarian Cancer, researchers will use blood samples before and after treatment to see if disease status can be determined by measuring the amount of biomarker.
Study to Assess the Effectiveness of the CAAb Test With Ovarian Cancer Patients	NCT00327925	Hayka, A.	Unknown	Women with ovarian cancer	Ovarian Cancer Associated Antibodies (CAAb)	The expectation of the CAAb in the cancer population differs from that of the control population
Mesothelin as a New Tumor Marker for Ovarian Cancer	NCT00155740	Chen, C.	Unknown	Women with ovarian cancer vs. benign adnexal pathology	mesothelin	We will evaluate that if mesothelin can be a new potential tumor marker for ovarian cancer in this proposal. We will evaluate the amount of mesothelin in pre- and post-treatment serum samples of patients with epithelial ovarian cancer. We will also correlate the clinicopathologic items and the prognosis of ovarian cancer patients and evaluate whether mesothelin can be a new tumor marker for ovarian cancer patients.

Table 3. Ongoing Clinical Trials (as of June 2011).

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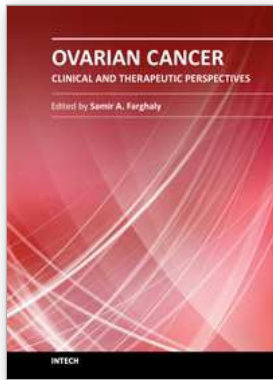
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Worldwide, Ovarian carcinoma continues to be responsible for more deaths than all other gynecologic malignancies combined. International leaders in the field address the critical biologic and basic science issues relevant to the disease. The book details the molecular biological aspects of ovarian cancer. It provides molecular biology techniques of understanding this cancer. The techniques are designed to determine tumor genetics, expression, and protein function, and to elucidate the genetic mechanisms by which gene and immunotherapies may be perfected. It provides an analysis of current research into aspects of malignant transformation, growth control, and metastasis. A comprehensive spectrum of topics is covered providing up to date information on scientific discoveries and management considerations.

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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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