2

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 recurrence[8-12]. Therapeutic vaccinations, targeting molecules specific to an individuals' 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 treatment [15]. 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 annually [1]. Further, ovarian cancer is the fifth most common cause of cancer mortality and remains the most lethal gynecologic cancer [1]. Platinum/taxane chemotherapy is available for women with this disease, and approximately 70-80% will respond to this regimen [1]. 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 prognosis [1]. 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 incidence [19]. 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 mortality [21].

While it is known that persistent HPV infection is responsible for virtually all cervical cancer and its immediate precursors worldwide [23], 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 rapidly [28]. 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 instability [24]. 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 process [19]. 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 consequences [37].

However, pelvic examination is generally recommended only for the evaluation of symptomatic patients and only in conjunction with ultrasonography [38]. 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 cancer [41].

In contrast, pelvic examination is recommended for disease surveillance of ovarian cancer per the NCCN guidelines, as 26-50% of recurrences occur within the pelvis [42]. 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 thorax [45].

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 uterus[46]. Primary screening studies with TVUS in both asymptomatic and symptomatic at-risk women have been successful in identifying early stage ovarian cancers [47-50].

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 women [51]; the upper limit of normal ovarian volume is 20 cm^3 and 10cm^3 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 screening [54]. 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 flow [53]. 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 physician [82].

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 disease [83-87]. 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 introduced into clinical practice [89].

Evolving technologies, including transcriptomics [84], epigenomics [85, 86], metabolomics [90] and glycomics [87], 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 tissue [84]. 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 screening [84].

Epigenomics focuses on the role of DNA methylation, histone modifications, RNA interference and nucleosome remodeling in the development and progression of ovarian cancer [86]. Epigenetic alterations can be used as candidate targets for early detection and for monitoring of ovarian cancer recurrence [85]. 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 tumorigenesis [85].

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 disease [90]. Lysophosphatidic acid [91] and lipid associated sialic acid [92] 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 MUC1 [93], 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 responses [94]. Therefore, glycoproteins are currently being examined for their potential as biomarker as well as for treatment [87].

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 women 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 cancer[117]. 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 women [121]. 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 1999 [122]. 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 cancers [41]. 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 hysterectomy [123]. 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 complications [21]. The results of this trial suggest that routine screening with CA125 and TVS 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 2005 [58]. 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 surveillance [36]. 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 disease [2]. Immune-driven vaccines are currently under investigation for the prevention of ovarian cancer recurrence [8-12].

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 responses [14]. 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 antigens [140]. 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 cells [142]. 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) response [143]. 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 months [144]. 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 Network 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 rumor marker for ovarian cancer patients.

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

7. References

[1] Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin;60:277-300.
[2] Cannistra SA. Cancer of the ovary. N Engl J Med 2004;351:2519-29.
[3] Etzioni R, Urban N, Ramsey S, et al. The case for early detection. Nat Rev Cancer 2003;3:243-52.
[4] Husseinzadeh N. Status of tumor markers in epithelial ovarian cancer has there been any progress? A review. Gynecol Oncol 2011;120:152-7.
[5] Scholler N, Lowe KA, Bergan LA, et al. Use of yeast-secreted in vivo biotinylated recombinant antibodies (Biobodies) in bead-based ELISA. Clin Cancer Res 2008;14:2647-55.
[6] Scholler N, Gross JA, Garvik B, et al. Use of cancer-specific yeast-secreted in vivo biotinylated recombinant antibodies for serum biomarker discovery. J Transl Med 2008;6:41.

[7] Liu B, Nash J, Runowicz C, Swede H, Stevens R, Li Z. Ovarian cancer immunotherapy: opportunities, progresses and challenges. J Hematol Oncol 2010;3:7.
[8] Benencia F, Courreges MC, Coukos G. Whole tumor antigen vaccination using dendritic cells: comparison of RNA electroporation and pulsing with UV-irradiated tumor cells. J Transl Med 2008;6:21.
[9] Chianese-Bullock KA, Irvin WP, Jr., Petroni GR, et al. A multipeptide vaccine is safe and elicits T-cell responses in participants with advanced stage ovarian cancer. J Immunother 2008;31:420-30.
[10] Tsuda N, Mochizuki K, Harada M, et al. Vaccination with predesignated or evidence-based peptides for patients with recurrent gynecologic cancers. J Immunother 2004;27:60-72.
[11] Aoki Y, Takakuwa K, Kodama S, et al. Use of adoptive transfer of tumor-infiltrating lymphocytes alone or in combination with cisplatin-containing chemotherapy in patients with epithelial ovarian cancer. Cancer Res 1991;51:1934-9.
[12] Fujita K, Ikarashi H, Takakuwa K, et al. Prolonged disease-free period in patients with advanced epithelial ovarian cancer after adoptive transfer of tumor-infiltrating lymphocytes. Clin Cancer Res 1995;1:501-7.
[13] Courreges MC, Benencia F, Conejo-Garcia JR, Zhang L, Coukos G. Preparation of apoptotic tumor cells with replication-incompetent HSV augments the efficacy of dendritic cell vaccines. Cancer Gene Ther 2006;13:182-93.
[14] Kandalaft LE PJD, Lori Smith, et al. Autologous whole-tumor antigen combinatorial immunotherapy for recurrent ovarian cancer. In: Society of Gynecologic Oncologists Annual Meeting on Women's Cancer March 14-17, 2010; San Francisco, CA.
[15] Wilson JM, Jungner YG. [Principles and practice of mass screening for disease]. Bol Oficina Sanit Panam 1968;65:281-393.
[16] Schwartz PE. Current diagnosis and treatment modalities for ovarian cancer. Cancer Treat Res 2002;107:99-118.
[17] Lu KH, Patterson AP, Wang L, et al. Selection of potential markers for epithelial ovarian cancer with gene expression arrays and recursive descent partition analysis. Clin Cancer Res 2004;10:3291-300.
[18] Scarinci IC, Garcia FA, Kobetz E, et al. Cervical cancer prevention: new tools and old barriers. Cancer 2010;116:2531-42.
[19] Clarke-Pearson DL. Clinical practice. Screening for ovarian cancer. N Engl J Med 2009;361:170-7.
[20] Badgwell D, Bast RC, Jr. Early detection of ovarian cancer. Dis Markers 2007;23:397-410.
[21] Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA 2011;305:2295-303.
[22] Nossov V, Amneus M, Su F, et al. The early detection of ovarian cancer: from traditional methods to proteomics. Can we really do better than serum CA-125? Am J Obstet Gynecol 2008;199:215-23.
[23] Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet 2007;370:890-907.
[24] Kurman RJ, McConnell TG. Precursors of endometrial and ovarian carcinoma. Virchows Arch 2010;456:1-12.

[25] Schorge JO, Modesitt SC, Coleman RL, et al. SGO White Paper on ovarian cancer: etiology, screening and surveillance. Gynecol Oncol 2010;119:7-17.
[26] Crum CP, Drapkin R, Kindelberger D, Medeiros F, Miron A, Lee Y. Lessons from BRCA: the tubal fimbria emerges as an origin for pelvic serous cancer. Clin Med Res 2007;5:35-44.
[27] Kindelberger DW, Lee Y, Miron A, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. Am J Surg Pathol 2007;31:161-9.
[28] Shih Ie M, Kurman RJ. Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. Am J Pathol 2004;164:1511-8.
[29] Vine MF, Calingaert B, Berchuck A, Schildkraut JM. Characterization of prediagnostic symptoms among primary epithelial ovarian cancer cases and controls. Gynecol Oncol 2003;90:75-82.
[30] . (Accessed June 25, 2011, at http://www.wcn.org/articles/types_of_cancer/ovarian/symptoms/index.html.)
[31] Goff BA, Mandel LS, Drescher CW, et al. Development of an ovarian cancer symptom index: possibilities for earlier detection. Cancer 2007;109:221-7.
[32] Goff BA, Mandel LS, Melancon CH, Muntz HG. Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. JAMA 2004;291:2705-12.
[33] Olson SH, Mignone L, Nakraseive C, Caputo TA, Barakat RR, Harlap S. Symptoms of ovarian cancer. Obstet Gynecol 2001;98:212-7.
[34] Rossing MA, Wicklund KG, Cushing-Haugen KL, Weiss NS. Predictive value of symptoms for early detection of ovarian cancer. J Natl Cancer Inst 2010;102:222-9.
[35] Lurie G, Wilkens LR, Thompson PJ, Matsuno RK, Carney ME, Goodman MT. Symptom presentation in invasive ovarian carcinoma by tumor histological type and grade in a multiethnic population: a case analysis. Gynecol Oncol 2010;119:278-84.
[36] Geurts SM, de Vegt F, van Altena AM, et al. Considering early detection of relapsed ovarian cancer: a review of the literature. Int J Gynecol Cancer 2011;21:837-45.
[37] Westhoff CL, Jones HE, Guiahi M. Do new guidelines and technology make the routine pelvic examination obsolete? J Womens Health (Larchmt) 2011;20:5-10.
[38] Committee Opinion No. 477: the role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer. Obstet Gynecol 2011;117:742-6.
[39] Westhoff C, Clark CJ. Benign ovarian cysts in England and Wales and in the United States. Br J Obstet Gynaecol 1992;99:329-32.
[40] Grover SR, Quinn MA. Is there any value in bimanual pelvic examination as a screening test. Med J Aust 1995;162:408-10.
[41] Buys SS, Partridge E, Greene MH, et al. 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;193:1630-9.
[42] Morgan RJ, Jr., Alvarez RD, Armstrong DK, et al. Ovarian cancer. Clinical practice guidelines in oncology. J Natl Compr Canc Netw 2008;6:766-94.
[43] von Georgi R, Schubert K, Grant P, Munstedt K. Post-therapy surveillance and after-care in ovarian cancer. Eur J Obstet Gynecol Reprod Biol 2004;114:228-33.
[44] Fehm T, Heller F, Kramer S, Jager W, Gebauer G. Evaluation of CA125, physical and radiological findings in follow-up of ovarian cancer patients. Anticancer Res 2005;25:1551-4.

[45] Gadducci A, Cosio S. Surveillance of patients after initial treatment of ovarian cancer. Crit Rev Oncol Hematol 2009;71:43-52.
[46] Ueland FR, Depriest PD, Desimone CP, et al. The accuracy of examination under anesthesia and transvaginal sonography in evaluating ovarian size. Gynecol Oncol 2005;99:400-3.
[47] Sato S, Yokoyama Y, Sakamoto T, Futagami M, Saito Y. Usefulness of mass screening for ovarian carcinoma using transvaginal ultrasonography. Cancer 2000;89:582-8.
[48] Bourne TH, Campbell S, Reynolds KM, et al. Screening for early familial ovarian cancer with transvaginal ultrasonography and colour blood flow imaging. BMJ 1993;306:1025-9.
[49] van Nagell JR, Jr., DePriest PD, Ueland FR, et al. Ovarian cancer screening with annual transvaginal sonography: findings of 25,000 women screened. Cancer 2007;109:1887-96.
[50] van Nagell JR, Jr., DePriest PD, Reedy MB, et al. The efficacy of transvaginal sonographic screening in asymptomatic women at risk for ovarian cancer. Gynecol Oncol 2000;77:350-6.
[51] Pavlik EJ, DePriest PD, Gallion HH, et al. Ovarian volume related to age. Gynecol Oncol 2000;77:410-2.
[52] Granberg S, Wikland M, Jansson I. Macroscopic characterization of ovarian tumors and the relation to the histological diagnosis: criteria to be used for ultrasound evaluation. Gynecol Oncol 1989;35:139-44.
[53] Timmerman D, Valentin L, Bourne TH, Collins WP, Verrelst H, Vergote I. Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) Group. Ultrasound Obstet Gynecol 2000;16:500-5.
[54] DePriest PD, Shenson D, Fried A, et al. A morphology index based on sonographic findings in ovarian cancer. Gynecol Oncol 1993;51:7-11.
[55] DePriest PD, Varner E, Powell J, et al. The efficacy of a sonographic morphology index in identifying ovarian cancer: a multi-institutional investigation. Gynecol Oncol 1994;55:174-8.
[56] Timmerman D, Testa AC, Bourne T, et al. Simple ultrasound-based rules for the diagnosis of ovarian cancer. Ultrasound Obstet Gynecol 2008;31:681-90.
[57] Van Calster B, Timmerman D, Bourne T, et al. Discrimination between benign and malignant adnexal masses by specialist ultrasound examination versus serum CA-125. J Natl Cancer Inst 2007;99:1706-14.
[58] Menon U, Gentry-Maharaj A, Hallett R, et al. 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;10:327-40.
[59] Salani R BF, Fung M, Holschneider CH, Parker LP, Bristow RE and Goff BA. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. Am J Obstet Gynecol 2011;204:466-78.
[60] Zhu CS, Pinsky PF, Cramer DW, et al. A framework for evaluating biomarkers for early detection: validation of biomarker panels for ovarian cancer. Cancer Prev Res (Phila) 2011;4:375-83.

[61] Bast RC, Jr., Klug TL, St John E, et al. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. N Engl J Med 1983;309:883-7.
[62] Jacobs I, Bast RC, Jr. The CA 125 tumour-associated antigen: a review of the literature. Hum Reprod 1989;4:1-12.
[63] Einhorn N, Sjovall K, Knapp RC, et al. Prospective evaluation of serum CA 125 levels for early detection of ovarian cancer. Obstet Gynecol 1992;80:14-8.
[64] Vaidya AP, Curtin JP. The follow-up of ovarian cancer. Semin Oncol 2003;30:401-12.
[65] Prat A, Parera M, Adamo B, et al. Risk of recurrence during follow-up for optimally treated advanced epithelial ovarian cancer (EOC) with a low-level increase of serum CA-125 levels. Ann Oncol 2009;20:294-7.
[66] Rustin GJ, Nelstrop AE, Tuxen MK, Lambert HE. Defining progression of ovarian carcinoma during follow-up according to CA 125: a North Thames Ovary Group Study. Ann Oncol 1996;7:361-4.
[67] Anderson GL, McIntosh M, Wu L, et al. Assessing lead time of selected ovarian cancer biomarkers: a nested case-control study. J Natl Cancer Inst 2010;102:26-38.
[68] Cramer DW, Bast RC, Jr., Berg CD, et al. Ovarian cancer biomarker performance in prostate, lung, colorectal, and ovarian cancer screening trial specimens. Cancer Prev Res (Phila) 2011;4:365-74.
[69] Helzlsouer KJ, Bush TL, Alberg AJ, Bass KM, Zacur H, Comstock GW. Prospective study of serum CA-125 levels as markers of ovarian cancer. JAMA 1993;269:1123-6.
[70] McDonald JM, Doran S, DeSimone CP, et al. Predicting risk of malignancy in adnexal masses. Obstet Gynecol 2010;115:687-94.
[71] Menon U, Skates SJ, Lewis S, et al. Prospective study using the risk of ovarian cancer algorithm to screen for ovarian cancer. J Clin Oncol 2005;23:7919-26.
[72] McIntosh MW, Drescher C, Karlan B, et al. Combining CA 125 and SMR serum markers for diagnosis and early detection of ovarian carcinoma. Gynecol Oncol 2004;95:9-15.
[73] Schorge JO, Drake RD, Lee H, et al. Osteopontin as an adjunct to CA125 in detecting recurrent ovarian cancer. Clin Cancer Res 2004;10:3474-8.
[74] Woolas RP, Xu FJ, Jacobs IJ, et al. Elevation of multiple serum markers in patients with stage I ovarian cancer. J Natl Cancer Inst 1993;85:1748-51.
[75] Andersen MR, Goff BA, Lowe KA, et al. Use of a Symptom Index, CA125, and HE4 to predict ovarian cancer. Gynecol Oncol 2010;116:378-83.
[76] Rosen DG, Wang L, Atkinson JN, et al. Potential markers that complement expression of CA125 in epithelial ovarian cancer. Gynecol Oncol 2005;99:267-77.
[77] Sturgeon CM, Hoffman BR, Chan DW, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for use of tumor markers in clinical practice: quality requirements. Clin Chem 2008;54:e1-e10.
[78] Drapkin R, von Horsten HH, Lin Y, et al. Human epididymis protein 4 (HE4) is a secreted glycoprotein that is overexpressed by serous and endometrioid ovarian carcinomas. Cancer Res 2005;65:2162-9.
[79] Visintin I, Feng Z, Longton G, et al. Diagnostic markers for early detection of ovarian cancer. Clin Cancer Res 2008;14:1065-72.

[80] McIntosh M, Anderson G, Drescher C, et al. Ovarian cancer early detection claims are biased. Clin Cancer Res 2008;14:7574; author reply 7-9.
[81] Rustin GJ, van der Burg ME, Griffin CL, et al. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. Lancet 2010;376:1155-63.
[82] Society of Gynecologic Oncologists Statement on Use of CA125 for Monitoring Ovarian Cancer. (Accessed June 28, 2011, at *www.sgo.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=3664*.)
[83] Petricoin EF, Ardekani AM, Hitt BA, et al. Use of proteomic patterns in serum to identify ovarian cancer. Lancet 2002;359:572-7.
[84] Chon HS, Lancaster JM. Microarray-based gene expression studies in ovarian cancer. Cancer Control 2011;18:8-15.
[85] Maradeo ME, Cairns P. Translational application of epigenetic alterations: Ovarian cancer as a model. FEBS Lett 2011;585:2112-20.
[86] Maldonado L, Hoque MO. Epigenomics and ovarian carcinoma. Biomark Med 2010;4:543-70.
[87] Wang H, Wong CH, Chin A, et al. Integrated mass spectrometry-based analysis of plasma glycoproteins and their glycan modifications. Nat Protoc 2011;6:253-69.
[88] Kozak KR, Amneus MW, Pusey SM, et al. Identification of biomarkers for ovarian cancer using strong anion-exchange ProteinChips: potential use in diagnosis and prognosis. Proc Natl Acad Sci U S A 2003;100:12343-8.
[89] Zhang B, Barekati Z, Kohler C, et al. Proteomics and biomarkers for ovarian cancer diagnosis. Ann Clin Lab Sci 2010;40:218-25.
[90] Guan W, Zhou M, Hampton CY, et al. Ovarian cancer detection from metabolomic liquid chromatography/mass spectrometry data by support vector machines. BMC Bioinformatics 2009;10:259.
[91] Baker DL, Morrison P, Miller B, et al. Plasma lysophosphatidic acid concentration and ovarian cancer. JAMA 2002;287:3081-2.
[92] Schutter EM, Visser JJ, van Kamp GJ, et al. The utility of lipid-associated sialic acid (LASA or LSA) as a serum marker for malignancy. A review of the literature. Tumour Biol 1992;13:121-32.
[93] Vlad AM, Kettel JC, Alajez NM, Carlos CA, Finn OJ. MUC1 immunobiology: from discovery to clinical applications. Adv Immunol 2004;82:249-93.
[94] Taylor AD, Hancock WS, Hincapie M, Taniguchi N, Hanash SM. Towards an integrated proteomic and glycomic approach to finding cancer biomarkers. Genome Med 2009;1:57.
[95] Scholler N, Garvik B, Quarles T, Jiang S, Urban N. Method for generation of in vivo biotinylated recombinant antibodies by yeast mating. J Immunol Methods 2006;317:132-43.
[96] Bergan L, Gross JA, Nevin B, Urban N, Scholler N. Development and in vitro validation of anti-mesothelin biobodies that prevent CA125/Mesothelin-dependent cell attachment. Cancer Lett 2007;255:263-74.
[97] Brinton LA, Westhoff CL, Scoccia B, et al. Causes of infertility as predictors of subsequent cancer risk. Epidemiology 2005;16:500-7.

[98] Kallen B, Finnstrom O, Lindam A, Nilsson E, Nygren KG, Olausson PO. Malignancies among women who gave birth after in vitro fertilization. Hum Reprod 2011;26:253-8.

[99] Ness RB, Cramer DW, Goodman MT, et al. Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. Am J Epidemiol 2002;155:217-24.

[100] Rossing MA, Tang MT, Flagg EW, Weiss LK, Wicklund KG. A case-control study of ovarian cancer in relation to infertility and the use of ovulation-inducing drugs. Am J Epidemiol 2004;160:1070-8.

[101] Tortolero-Luna G, Mitchell MF. The epidemiology of ovarian cancer. J Cell Biochem Suppl 1995;23:200-7.

[102] Franceschi S, Parazzini F, Negri E, et al. Pooled analysis of 3 European case-control studies of epithelial ovarian cancer: III. Oral contraceptive use. Int J Cancer 1991;49:61-5.

[103] Negri E, Franceschi S, Tzonou A, et al. Pooled analysis of 3 European case-control studies: I. Reproductive factors and risk of epithelial ovarian cancer. Int J Cancer 1991;49:50-6.

[104] Kerlikowske K, Brown JS, Grady DG. Should women with familial ovarian cancer undergo prophylactic oophorectomy? Obstet Gynecol 1992;80:700-7.

[105] Boyd J. Molecular genetics of hereditary ovarian cancer. Oncology (Williston Park) 1998;12:399-406; discussion 9-10, 13.

[106] Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72:1117-30.

[107] Khoury-Collado F, Bombard AT. Hereditary breast and ovarian cancer: what the primary care physician should know. Obstet Gynecol Surv 2004;59:537-42.

[108] Lancaster JM, Powell CB, Kauff ND, et al. Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol 2007;107:159-62.

[109] Tan DS, Rothermundt C, Thomas K, et al. "BRCAness" syndrome in ovarian cancer: a case-control study describing the clinical features and outcome of patients with epithelial ovarian cancer associated with BRCA1 and BRCA2 mutations. J Clin Oncol 2008;26:5530-6.

[110] Barrow E, Robinson L, Alduaij W, et al. Cumulative lifetime incidence of extracolonic cancers in Lynch syndrome: a report of 121 families with proven mutations. Clin Genet 2009;75:141-9.

[111] *SEER Cancer Statistics Review, 1975-2008.*, 2011. (Accessed at http://seer.cancer.gov/csr/1975_2008/.)

[112] Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet 2008;371:303-14.

[113] Narod SA, Risch H, Moslehi R, et al. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. N Engl J Med 1998;339:424-8.

[114] La Vecchia C. Oral contraceptives and ovarian cancer: an update, 1998-2004. Eur J Cancer Prev 2006;15:117-24.

[115] Hinkula M, Pukkala E, Kyyronen P, Kauppila A. Incidence of ovarian cancer of grand multiparous women--a population-based study in Finland. Gynecol Oncol 2006;103:207-11.
[116] Antoniou AC, Rookus M, Andrieu N, et al. Reproductive and hormonal factors, and ovarian cancer risk for BRCA1 and BRCA2 mutation carriers: results from the International BRCA1/2 Carrier Cohort Study. Cancer Epidemiol Biomarkers Prev 2009;18:601-10.
[117] Jordan SJ, Siskind V, A CG, Whiteman DC, Webb PM. Breastfeeding and risk of epithelial ovarian cancer. Cancer Causes Control 2010;21:109-16.
[118] Danforth KN, Tworoger SS, Hecht JL, Rosner BA, Colditz GA, Hankinson SE. Breastfeeding and risk of ovarian cancer in two prospective cohorts. Cancer Causes Control 2007;18:517-23.
[119] Hankinson SE, Hunter DJ, Colditz GA, et al. Tubal ligation, hysterectomy, and risk of ovarian cancer. A prospective study. JAMA 1993;270:2813-8.
[120] Narod SA, Sun P, Ghadirian P, et al. Tubal ligation and risk of ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. Lancet 2001;357:1467-70.
[121] Jacobs IJ, Skates SJ, MacDonald N, et al. Screening for ovarian cancer: a pilot randomised controlled trial. Lancet 1999;353:1207-10.
[122] Kobayashi H, Yamada Y, Sado T, et al. A randomized study of screening for ovarian cancer: a multicenter study in Japan. Int J Gynecol Cancer 2008;18:414-20.
[123] Nyante SJ, Black A, Kreimer AR, et al. Pathologic findings following false-positive screening tests for ovarian cancer in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. Gynecol Oncol 2011;120:474-9.
[124] Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 1999;116:1453-6.
[125] Finch A, Beiner M, Lubinski J, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. JAMA 2006;296:185-92.
[126] Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst 2009;101:80-7.
[127] Anderson K, Jacobson JS, Heitjan DF, et al. Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation. Ann Intern Med 2006;144:397-406.
[128] Yang KY, Caughey AB, Little SE, Cheung MK, Chen LM. A cost-effectiveness analysis of prophylactic surgery versus gynecologic surveillance for women from hereditary non-polyposis colorectal cancer (HNPCC) Families. Fam Cancer 2011.
[129] Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med 2006;354:261-9.
[130] Kwon JS, Sun CC, Peterson SK, et al. Cost-effectiveness analysis of prevention strategies for gynecologic cancers in Lynch syndrome. Cancer 2008;113:326-35.
[131] van der Velde NM, Mourits MJ, Arts HJ, et al. Time to stop ovarian cancer screening in BRCA1/2 mutation carriers? Int J Cancer 2009;124:919-23.

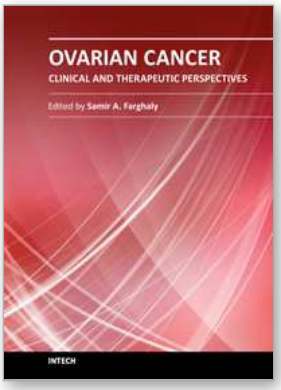
[132] Olivier RI, Lubsen-Brandsma MA, Verhoef S, van Beurden M. CA125 and transvaginal ultrasound monitoring in high-risk women cannot prevent the diagnosis of advanced ovarian cancer. Gynecol Oncol 2006;100:20-6.
[133] Auranen A, Joutsiniemi T. A systematic review of gynecological cancer surveillance in women belonging to hereditary nonpolyposis colorectal cancer (Lynch syndrome) families. Acta Obstet Gynecol Scand 2011;90:437-44.
[134] Moore RG, Jabre-Raughley M, Brown AK, et al. Comparison of a novel multiple marker assay vs the Risk of Malignancy Index for the prediction of epithelial ovarian cancer in patients with a pelvic mass. Am J Obstet Gynecol 2010;203:228 e1-6.
[135] Moore RG, McMeekin DS, Brown AK, et al. A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. Gynecol Oncol 2009;112:40-6.
[136] Montagnana M, Danese E, Ruzzenente O, et al. The ROMA (Risk of Ovarian Malignancy Algorithm) for estimating the risk of epithelial ovarian cancer in women presenting with pelvic mass: is it really useful? Clin Chem Lab Med 2011;49:521-5.
[137] Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas JG. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol 1990;97:922-9.
[138] Zhang L, Conejo-Garcia JR, Katsaros D, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. N Engl J Med 2003;348:203-13.
[139] Adams SF, Levine DA, Cadungog MG, et al. Intraepithelial T cells and tumor proliferation: impact on the benefit from surgical cytoreduction in advanced serous ovarian cancer. Cancer 2009;115:2891-902.
[140] Kandalaft LE, Powell DJ, Jr., Singh N, Coukos G. Immunotherapy for ovarian cancer: what's next? J Clin Oncol 2011;29:925-33.
[141] Buckanovich RJ, Facciabene A, Kim S, et al. Endothelin B receptor mediates the endothelial barrier to T cell homing to tumors and disables immune therapy. Nat Med 2008;14:28-36.
[142] Steinman RM. Dendritic cells: understanding immunogenicity. Eur J Immunol 2007;37 Suppl 1:S53-60.
[143] Cannon MJ, O'Brien TJ. Cellular immunotherapy for ovarian cancer. Expert Opin Biol Ther 2009;9:677-88.
[144] Hernando JJ, Park TW, Kubler K, Offergeld R, Schlebusch H, Bauknecht T. Vaccination with autologous tumour antigen-pulsed dendritic cells in advanced gynaecological malignancies: clinical and immunological evaluation of a phase I trial. Cancer Immunol Immunother 2002;51:45-52.
[145] Padilla LA, Radosevich DM, Milad MP. Limitations of the pelvic examination for evaluation of the female pelvic organs. Int J Gynaecol Obstet 2005;88:84-8.
[146] Greene MH, Piedmonte M, Alberts D, et al. A prospective study of risk-reducing salpingo-oophorectomy and longitudinal CA-125 screening among women at increased genetic risk of ovarian cancer: design and baseline characteristics: a Gynecologic Oncology Group study. Cancer Epidemiol Biomarkers Prev 2008;17:594-604.

[147] Jacobs I, Gentry-Maharaj A, Burnell M, et al. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. Lancet Oncol 2011;12:38-48.

[148] Lowe KA, Andersen MR, Urban N, Paley P, Dresher CW, Goff BA. The temporal stability of the Symptom Index among women at high-risk for ovarian cancer. Gynecol Oncol 2009;114:225-30.

[149] Lacey JV, Jr., Greene MH, Buys SS, et al. Ovarian cancer screening in women with a family history of breast or ovarian cancer. Obstet Gynecol 2006;108:1176-84.

[150] Partridge E, Kreimer AR, Greenlee RT, et al. Results from four rounds of ovarian cancer screening in a randomized trial. Obstet Gynecol 2009;113:775-82.



Ovarian Cancer - Clinical and Therapeutic Perspectives

Edited by Dr. Samir Farghaly

ISBN 978-953-307-810-6
Hard cover, 338 pages
Publisher InTech
Published online 15, February, 2012
Published in print edition February, 2012

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Gina M. Mantia-Smaldone and Nathalie Scholler (2012). Preventive Strategies in Epithelial Ovarian Cancer, Ovarian Cancer - Clinical and Therapeutic Perspectives, Dr. Samir Farghaly (Ed.), ISBN: 978-953-307-810-6, InTech, Available from: http://www.intechopen.com/books/ovarian-cancer-clinical-and-therapeutic-perspectives/preventive-strategies-against-epithelial-ovarian-cancer

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
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