Is CA-125 the Leading Biomarker in Determining Early-Onset Ovarian Cancer Diagnosis in 2016?

Alexa Clark
alexa_clark@my.uri.edu

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Honors Project Research Summary

Abstract:

Ovarian cancer is the most lethal gynecologic malignancy with very ineffective efforts at early detection and therapeutic methodologies to reduce mortality. The goal of my project is to gain a better understanding of the tumor marker CA-125 in relation to ovarian cancer and what steps are being made to better diagnosis early onset ovarian cancer. CA-125 marker is not specific or diagnostic for ovarian cancer, but is used for therapeutic reasons. This review will summarize current biomarkers and ongoing research performed to better diagnose early-onset ovarian cancer.

Title:

Is CA-125 the Leading Biomarker in Determining Early-Onset Ovarian Cancer Diagnosis in 2016?

Objectives:

The goal of this research is to determine why CA-125 is not a useful cancer screening test for ovarian cancer and discover other procedures and further research that are being performed to better diagnose early-onset ovarian cancer in asymptomatic patients.

APA Citation Abbreviations:

<table>
<thead>
<tr>
<th>Word</th>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>Cancer Antigen</td>
<td>CA</td>
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<tr>
<td>Human Epididymis Protein</td>
<td>HE4</td>
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<tr>
<td>Parametric Empirical Bayes</td>
<td>PEB</td>
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<td>Verses</td>
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**Introduction:**

Epithelian ovarian cancer is composed of different groups of tumors that are classified based on their diverse morphology and molecular genetic features: Type II and I. Type I is composed of low-grade serous, low-grade endometrioid, clear cell, mucinous, and transitional (Brenner) carcinoma. Type II ovarian cancer is highly aggressive, has high-grade serous carcinoma, undifferentiated carcinoma and malignant mixed mesodermal tumors (carcinosarcoma). Type II describes tumors that arise without macroscopic premalignant precursors, making it much harder to diagnose early on. Due to the late diagnosis and aggressive progression, Type II is associated with most ovarian cancer deaths.

The most common therapeutic tool used for ovarian cancer is CA-125. CA-125 is a high molecular weight trans-membrane glycoprotein that is expressed by coelomic- and Mullerian-derived epithelia, including the fallopian tube, endometrium, and endocervix. CA-125 is a therapeutic marker that is elevated in the blood of patients with ovarian cancer, but it is not diagnostic. This cancer marker is greater in concentration in ovarian cancer cells than in other cells, but not specific. The role of CA-125 in the early detection of ovarian cancer is extremely controversial and has not been widely accepted for screening in women that do not show any symptoms. CA-125 is currently only able to detect how the ovarian cancer is responding to treatment and how far along it is.

**Current Diagnosis of Ovarian Cancer:**

Only around 20% of ovarian cancers are found at an early age. If the cancer is found early, 94% of patients live longer than five years after diagnosis. Prognosis for ovarian cancer is excellent when the detection is at an early stage, but unfortunately this
does not happen frequently. This is why the need for an early diagnostic tool is significant for ovarian cancer. There are currently two tests that most often used to screen for ovarian cancer: transvaginal ultrasound (TVUS) and CA-125 blood test. [1] Both tests are not recommended by major medical or professional organizations for routinely screening ovarian cancer due to their inaccuracy. TVUS uses sound waves to look at the uterus, fallopian tubes, and ovaries through using an ultrasound wand. It is able to find a mass in the ovary, but it cannot determine if a mass is cancer or benign.

The CA-125 blood test has not been found useful due to other common conditions than cancer causing high levels of CA-125. Also, not everyone with ovarian cancer have a high CA-125 level. This marker is not only elevated in ovarian cancer, but also elevated in benign conditions, such as endometriosis, diseases of the ovary, and menstruation. The CA-125 marker can also be elevated in endometrial cancer, fallopian tube cancer, lung cancer, breast cancer, and gastrointestinal cancer, proving that it is not specific for just ovarian cancer and cannot be solely used as a diagnostic tool without another tumor marker. I seek to find out what other tumor markers are substantial in diagnosing early onset ovarian cancer regarding the tumor marker CA-125.

**Overview/Methodology:**

In order to enhance the sensitivity for early disease detection there have been three notable advances taken. The first approach is obtaining longitudinal measurements of CA-125 to calculate the probability of ovarian cancer for a patient using the Bayesian algorithm. A longitudinal algorithm involves the change over time in biomarker levels in order to individualize screening decision rules. In comparison to a single-threshold (ST) rule, smaller deviations from the baseline biomarker levels are made to signal the disease.
In this longitudinal algorithm, serial preclinical serum Ca-125 values were measured annually in 44 incident ovarian cancer cases that were identified from participants in the PLCO (Prostate Lung Colorectal and Ovarian) Cancer Screening Trial. The CA-125 values were used to determine how frequent the parametric empirical Bayes (PEB) longitudinal screening algorithm could identify ovarian cancer earlier than a single-threshold (ST) rule. [2]

The second approach uses algorithms to research CA125 and HE4’s significance to diagnosing ovarian cancer. Tumor marker human epididymis protein (HE4) was used in combination with CA125 to screen asymptomatic women in the general population. HE4 is found primarily in the epithelia of normal genital tissues and is made up of a four disulfide core and two whey acidic proteins. HE4 is elevated in epithelial cancer, but this research determines the specificity and sensitivity in correlation to CA125. HE4 and CA125 were analyzed through genomic strategies and the development of algorithms Risk of Malignancy Algorithm (ROMA), OVA1, compared to Risk of Malignancy Index (RMI). RMI, developed in 1990 by Jacobs et al, is a formula which incorporates a woman’s CA125 level, ultrasound score, and menopausal status in order to figure out their likelihood of malignancy for the adnexal mass. The recent algorithms developed, ROMA and OVA1 are used to evaluate the effectiveness of RMI. ROMA algorithm is based on the serum level of HE4 and CA-125 with menopausal status. OVA1 is made up of biomarkers through mass spectrometry: β-2 microglobulin, transferrin, transthyretin, and apolipoprotein.

The third approach determined other significant biomarkers that can increase the sensitivity and specificity of CA125, in comparison with HE4. This final approach
assembles panels of biomarkers to create a “composite marker.” Due to CA125 levels occurring in various benign gynecologic conditions, this approach identifies other novel biomarkers that can increase the sensitivity and specificity of CA125 through analysis of adnexal masses in two hundred and fifty-nine patients.

**Pathogenesis:**

The overall survival of women with ovarian cancer has not changed in over 50 years because most screening studies have been unsuccessful in providing a survival benefit or early diagnostic tool. Currently, most management is directed at cancers that are already developed rather than the mechanism of how cancers come about. Fortunately, in the last few years there have been significant advances in the field, increasing our understanding of ovarian cancer, to improve the outcome [3].

Ovarian cancer originates from ovarian surface epithelium (mesothelium), which invaginates into underlying stroma that results in inclusion cysts. Inclusions cysts undergo malignant transformation after they are produced, but this origin and pathogenicity is still vastly unclear, which is why diagnosing the disease early on is difficult. It is proposed that ovarian cancer develops de novo “nothing will come from nothing.” Each year in the United States approximately 21,550 women develop ovarian cancer “de novo” and 14,600 women die from ovarian cancer [4]. Although there are significant differences between the histologic types of ovarian cancer, the majority of ovarian carcinomas are high-grade serious carcinomas. Ovarian cancer can spread from the ovary to the abdomen, pelvis, and other distant sites.
Relevant Laboratory Data/Discussion:

At 99% specificity, the PEB algorithm detected ovarian cancer earlier than a ST rule in 20% of cases. A CA-125 cutoff of greater than/or equal to 35 U/mL was used. Among the 20% of cases, PEB signaled abnormal CA-125 values, at about 10 months earlier and at a CA-125 concentration 42% (20U/mL) lower than ST-rule cutoff [2]. Not only was this test able to increase the amount of cases diagnosed earlier than normal, it is also able to decrease the amount of concentration needed to do so. With use of the PEB algorithm, ovarian cancer could potentially be diagnosed 10 months earlier, creating a much greater prognosis for the patients.
Graph 1: Participant vs. Time to Diagnosis (years) [2].
Graph 1 represents the screening histories for the 44 incident PLCO Cancer screening trial ovarian cancer patient cases with two consecutive screens and who’s proximate screen falls within the year diagnosed. The numerical values are a representation of CA-125 concentrations. The blue concentrations are positive for PEB and ST rules at 99% specificity and the black concentrations are negative. The red numerical values are PEB positive and ST negative at 99% specificity.

Through the second approach, HE4 proved to significantly increase the specificity with CA-125. Through genomic strategies, HE4 had a similar sensitivity (79%) to CA-125 but demonstrated a higher specificity (93% vs. 78%) to CA-125 when distinguishing between benign diseases from ovarian cancer. HE4 has greater specificity in premenopausal age groups than CA-125 because it is not expressed at high levels in the setting of benign conditions such as endometriosis. Still, it is unlikely an individual biomarker will reach a specificity of 99.6%, positive predictive value of 10%, and sensitivity greater than 75% when screening an asymptomatic general population [5]. Progress has been made through developing algorithms to eliminate malignancy with using an adnexal mass. Through ROMA and OVA-1, HE4 is also superior to CA-125 with or without RMI and ROMA indices. HE4 has 98% sensitivity and 100% specificity for the detection of ovarian cancer. There is no benefit from combining both markers in ROMA and OVA-1[6].

The third approach demonstrated a potential benefit in combining HE4 and CA125 to create a composite marker and quantify risk potential malignancy in the evaluation of an adnexal mass through analyzing the levels of different biomarkers in their relation to their specificity. The samples analyzed were CA125, SMRP, HE4,
CA72-4, activin, inhibin, osteopontin, epidermal growth factor (EGFR), and ERBB2 (Her2). Out of all the combinations, CA-125 and HE-4 yielded the highest sensitivity at 76.4% (specificity 95%). Alone, HE4 had the highest sensitivity at 72.9% (specificity 95%), and no other markers made a substantial significance as a single marker. The best marker for Stage 1 disease was HE4, and there was no increase in sensitivity with CA-125 or any other marker [6].

**Case Conclusion:**

For ovarian cancer screening by using CA125, the PEB longitudinal algorithm detected ovarian cancer earlier than an ST rule proving its statistical significance in several cases. The PEB longitudinal algorithm identifies ovarian cancer 10 months earlier and at lower biomarker concentrations in CA-125 than in ST screening algorithm at the same specificity. The longitudinal biomarker assessment through the PEB algorithm could potentially be used to screen other solid tumors where biomarkers are available. This algorithm shows potential promise for future diagnosis of early-onset ovarian cancer. The algorithm is computationally simply, easy to use, and readily adaptable to many different biomarkers and screening programs that use early recall [7].

Through the genomic approaches, HE4 is proved to be a more specific biomarker than CA-125 in diagnosing ovarian cancer in patients with pelvic and adnexal masses and represents a victory for genomic strategies in the search for effective biomarkers in the prediction of malignancy. As a single tumor marker, HE4 had the highest sensitivity for detecting stage I disease of ovarian cancer. Although HE4 is more specific than CA-125, combined they are more accurate predictors of malignancy than either alone. Still, more research needs to be done on increasing the specificity and sensitivity in the
asymptomatic population.

Ca-125 remains a valued tool for monitoring the response to chemotherapy and detecting disease relapse after treatment of ovarian cancer. Longer-term studies of CA-125 are still underway and focusing on identifying the origin of tumor groups will lead to more effective screening strategies in asymptomatic populations and improved categorization through molecular advances will help to better approximate the time course of ovarian cancer. In order to identify early stage disease of ovarian cancer, there will need to be a change in the current approaches to include advances made in the understanding of tumor heterogeneity in this malignancy. Through the different approaches of research, it is clear that the combination of HE4 with CA125 shows promise for future diagnoses of early onset ovarian cancer and more research should be conducted on the composite marker in order to best diagnose the patient.
References:


