

Diagnostic Performance of CA125 for Detection of Ovarian Cancer

Saswati Satapathy^{1*}, Soubhagyalaxmi Dhal², Asmita Rout³

¹Assistant Professor, Department of Paramedical and Allied Sciences, DRIEMS University, Cuttack, India

Email: satapathysaswati8@gmail.com

Contact: +91-7008957150

²Assistant Professor, Department of Paramedical and Allied Sciences, DRIEMS University, Cuttack, India

Email: soubhagyalaxmidhal72@gmail.com

Contact: +91-9861664492

³Assistant Professor, Department of Paramedical and Allied Sciences, DRIEMS University, Cuttack, India

Email: asmitarout3627@gmail.com

Contact: +91-7008163101

***Corresponding Author:** Saswati Satapathy, Assistant Professor, Department of Paramedical and Allied Sciences, DRIEMS University, Cuttack, India
Email: satapathysaswati8@gmail.com

Abstract

The second most fatal gynecological cancer is ovarian cancer. For the past four decades, the predominant ovarian cancer marker has been the tumor biomarker CA125. According to the dualistic model of ovarian cancer carcinogenesis, type II tumors are mostly to blame for ovarian cancer mortality. However, Stages I and II are rarely used for the diagnosis of type II cancers. For symptomatic women, the blood biomarker cancer antigen 125 (CA125) is frequently used to check for potential ovarian cancer. We assessed CA125's effectiveness in the identification of ovarian and other malignancies. 50,780 women in total had CA125 testing; 456 (0.9%) received an ovarian cancer diagnosis and 1,321 (2.6%) received a non-ovarian cancer diagnosis. 3.4% of women under the age of 50 and 15.2% of women over the age of 50 who had a CA125 level of 35 U/ml had ovarian cancer of females 20.4% of individuals with a CA125 level of 35 U/ml who were 50 years of age or older and did not have ovarian cancer had a non-ovarian cancer diagnosis. A CA125 reading of 53 U/ml indicated a 3% chance of overall ovarian cancer. Depending on age, this had a value of 104 U/ml in 0-year-old women and 32 U/ml in 70-year-old women equating to a 3% probability. In primary care, the CA125 test is helpful for finding ovarian cancer, especially in women over 50. In order to avoid diagnostic errors, doctors should also take non-ovarian malignancies into account in women with high CA125 values, especially if ovarian cancer has been ruled out. Our findings allow clinicians and patients to estimate the likelihood of ovarian cancer and all cancers at any age and CA125 level.

Keywords: CA125, Ovarian cancer, Biomarker, Malignancy, Diagnosis

How to cite this article: Saswati Satapathy^{1*}, Soubhagyalaxmi Dhal², Asmita Rout³. Diagnostic Performance of CA125 for Detection of Ovarian Cancer. Int J Drug Deliv Technol. 2026;16(84s):379-388. DOI: 10.25258/ijddt.16.84s.44.

1. Introduction

The only serological biomarker routinely used for the therapy of patients with epithelial, ovarian, fallopian tube, or primary serous peritoneal cancer is cancer antigen (CA 125). *Bob Bast* and his associates discovered OC 125, an antibody that recognizes CA 125. The discovery of CA 125 as a circulating antigen paved the way for potentially crucial field of ovarian cancer biomarker research. The majority of epithelial ovarian malignancies do not become clinically apparent until later in life and only a mere 25% of cancers are detected as stage I disease which with currently available cyto reductive surgery and combination chemotherapy can approach 90% cure rate. [1]

Ovarian cancer is the seventh most prevalent type of cancer among women worldwide. Stage I have a five-year net survival rate of 93%, stage II has a six-year net survival rate of 68%, stage III has a five-year net survival rate of 27%, and stage IV has a 13.4% five-year net survival rate. As symptoms can appear at any

stage of ovarian cancer, the majority of women are identified after experiencing them.

Chemotherapy has been proven to be a successful treatment for ovarian cancer, a condition that nonetheless results in death for the majority of patients. Despite the success of high response rates following surgery and chemotherapy, 75% of women eventually pass away from problems brought on by the disease's development. Even with effective therapy, the survival rate for stage III and stage IV ovarian cancer, which is defined by peritoneal and extraperitoneal metastatic dissemination, drops from 95% at stage I to about 20–25% at five years. [2]

When cells undergo meta plastic differentiation into a Mullerian-type epithelium, CA 125 is produced as a membrane-bound protein at their surface or secreted in soluble form into body fluids. The concentration of CA125 in bodily fluids corresponds to specific physical situations which helps in early identification of ovarian cancer. The first generation of diagnostic

assays could be made using only one mAb in the roles of both capture and detection directed against the OC125-like epitope because of the complex structure of CA125. 35k U/L or less serves as the CA125 reference interval. Healthy premenopausal women may experience elevated amounts after menstruation, during pregnancy, and in non-malignant gynecologic conditions such as ovarian cysts, endometriosis, adenomyosis, and uterine leiomyomas. 80% of women with epithelial ovarian cancer have concentrations higher than 35k U/L, with 50% to 0% of patients having clinical stage I illness, 80% to 90% having stage II disease, and more than 90% having stage III to IV disease. [3]

1.1 Problem Statement Of the Thesis

For the past four decades, the most prevalent ovarian cancer marker has been the tumor biomarker CA125 as it examines our blood for certain proteins, and ovarian cancer may be the source of those proteins. The CA125 test is useful in detecting ovarian cancer, particularly among women over the age of 50 but using CA 125 as a diagnostic biomarker to diagnose ovarian cancer in stages I and II has not boosted patient survival. According to the dualistic model screen of CA125 carcinogenesis, type II tumors are mostly accountable for ovarian cancer mortality. However, it is hard to see type II tumors in stage I and II. [4]

1.2 Objective

To investigate the CA125 test's diagnostic effectiveness in AHPGIC women based on a woman's age and CA125 level. To evaluate the importance of CA 125 changes within reference levels in ovarian cancer patients who had full remissions following first-line therapy.

2. Literature Survey

2.1 Introduction of CA125

2.1.1 Role as a Biomarker for Detection

The natural history of OC has only just begun to be well understood because of the meticulous analysis of tissue from women who had preventive surgery or been through oral contraceptives. During preventative surgery, the fimbriae end of the fallopian tube (FT) is usually found with a known mutation in BRCA1 or BRCA2, along with intraepithelial cancer or dysplasia in women. These findings imply that the tubal intraepithelial carcinoma (TIC) or tubal dysplasia may serve as precursor lesions for serous OC that may develop inside the FT in mutation carriers.

2.1.2 As a clinical biomarker

CA125 has been extensively investigated as a biomarker in three separate clinical scenarios: As a screening test for the early detection of ovarian cancer, (2) to distinguish between benign and malignant disease in pre- and postmenopausal women presenting

with pelvic masses, and (3) to monitor response to therapy in women with ovarian cancer. [5]

2.1.3 As a screening modality

Based on long-term CA125 monitoring, the Risk of Ovarian Cancer Algorithm (ROCA) forecasts the likelihood of developing ovarian cancer that enables the stratification of patients into low, middle, and high-risk OC groups.

ROCA was created following a retrospective examination of serum samples from AHPGIC data storage that screened 5550 women for ovarian cancer. This experiment came to the conclusion that postmenopausal women got benefited most from serum CA125 monitoring. With a cohort of 10,000 women, the largest fully reported ovarian cancer screening experiment that used CA125 as a biomarker (in conjunction with ultrasonography) was carried out at the Acharya Harihar Post Graduation Institute of Cancer. Based on CA125 and ultrasonography, ovarian cancer was detected in a total of 41 women. After further surgical investigation, only eleven of these 41 patients were proven to be genuinely positive for ovarian cancer. Eight women who had initially tested negative for ovarian cancer went on to develop the condition 12 to 22 months later. [6,7]

2.1.4 As a diagnostic marker

A rise in CA125 concentration above the nadir is a sign of illness recurrence. Separating benign pelvic masses from ovarian cancer is a crucial potential use of the CA125 assay. The Risk of Malignancy Index (RMI) uses ultrasound, menopausal state, and serum CA125 concentrations to differentiate between benign illness and malignancy. According to recent research, a test with high sensitivity and specificity for detecting ovarian cancer patients would likely be produced by a Risk of Ovarian Malignancy Algorithm (ROMA) that incorporates serum levels of CA125 and HE4 (as a diagnostic indicator for ovarian cancer other from CA125).

In light of the findings from the experiments of PLCO, it is concluded that CA125 will continue to be the most prevalent and clinically significant biomarker for ovarian cancer for the foreseeable future. [8]

2.2 Biomarker Based Algorithm

It is believed that algorithms that combine CA125 using serum biomarker measures, age, and menopausal status are more useful than CA125 alone for ovarian cancer screening. Menopausal status, fixed threshold (35 U/mL) CA125 levels and ultrasound results were all incorporated into a logistic model by the risk of malignancy index (RMI). An RMI threshold of 250 resulted in a promising sensitivity of 88% and specificity of 74% for the preoperative categorization of benign vs. malignant adnexal masses, according to research, OVA1 is a second panel of five biomarkers, including CA125,

Transthyretin, Apolipoprotein A1, Transferrin and B2-microglobulin that are used to discriminate between individuals with pelvic masses who are at high and low risk of developing ovarian cancer.

2.2.1 Screening with single biomarker

It measures at defined thresholds is regarded as inferior to longitudinal screening procedures employing biomarker-based algorithms. 10,000 postmenopausal women participated in an AWI experiment to assess the effectiveness of ovarian cancer multimodal screening utilizing sequential CA125 levels and transvaginal ultrasonography. [9,10] The screening arm's median survival for cancer patients was longer than the control arm's (72.9 months vs. 41.8 months, $p = 0.0112$). The number of ovarian cancer fatalities in the two groups, however, showed no discernible difference. An algorithm for calculating cancer risk using hierarchical change point and mixture models was created using the same dataset. It has been demonstrated that employing a longitudinal CA125 screening technique has higher sensitivity than using fixed cutoffs. Serial CA125 values in patients often increase with ovarian cancer, whereas serial biomarker levels tend to stay close to the baseline for those with benign diseases or healthy women. As a result, rather than employing a predetermined cutoff, the risk of ovarian cancer algorithm (ROCA) was created using variations in successive CA125 readings. This algorithm divides patients into various follow-up groups and emphasizes rapid increases in biomarker levels. [11]

Transvaginal sonography (TVS) and the serum marker CA125 are usually performed every 6 to 12 months. Although most occult tumors in women are detected during preventive surgery and roughly 50% of clinically diagnosed stage I cases have pre-operative CA125 levels below the standard cut-off of 35U/ml, ca125 is elevated in the serum of most women with ovarian cancer (OC). [12]

Similar concerns exist about transvaginal sonography's ability to identify OC while it is still curable, because many women with advanced stage show normal appearing ovaries on TVS just 3-12 months before clinical diagnosis. OC often progresses despite regular screening in the high-risk group when TVS detects it. In a study screening over 6000 HR women with CA125 and TVS, only 38 OC cases were found, out of which only 9 were stage-I. both the tests are not able to detect 15 malignancies that have been discovered after a year of screening. [13][Table 1]

GROUP	TOTAL NO. TESTED	ANTIGEN LEVEL [IN NO. %]
		>35 U/ml >65 U/ml

Apparently healthy controls	888	9(1.0) 2(0.2)
Males	537	4(0.7) 2(0.4)
females	351	5(1.4) 0(0.0)
Patient with benign diseases	143	9(6.3) 3(2.1)
Patients with non-gynaecological cancer	200	57(28.5) 44(22.0)
pancreatic	29	17(58.6) 13(44.8)
lung	25	8(32.0) 6(24.0)
Breast	25	3(12.0) 2(8.0)
colorectal	71	16(22.5) 12(16.9)
Misc. gastrointestinal	30	8(26.7) 6(20.0)
Misc. non-gastrointestinal	20	5(25.0) 5(25.0)
Patients with ovarian carcinoma	101	83(82.2) 75(74.3)

Table 1: detection of CA 125 antigen in serum level of patients

2.3 Uses for Risk of Ovarian Cancer

Two decades ago, 323 matched controls and 105 women who later got ovarian cancer had their CA125 levels in AHPGIC examined. Women with OC had median CA125 values of 18.0 over the five years of preceding diagnosis, compared to only 10.9 in healthy women. After a median of 18 months since diagnosis, CA125 was 27.2. The same data were used in case-control research, which revealed that CA125 is above 30 U/ml in 50% and 24% of patients respectively up to 18 and 60 months before diagnosis. [14]

2.4 Factors Influencing Serum CA125 Concentrations

Normal serum concentrations of the ovarian tumor marker are influenced by many physiological variables. Post-menopausal women have notably higher levels than pre-menopausal women, and values rise with tumor burden and FIGO stage in ovarian cancer. However, numerous benign conditions (such as endometriosis, ovarian cysts or pelvic inflammation) also elevate the marker causing many false positives, only about 20% of ovarian tumors show an elevated reading during screening, meaning 80% of high values are cancer-free. The marker is useful for detecting moderate to severe endometriosis.

levels increase during menstrual cycle and higher in an ovulatory healthy woman. Pregnancy raises the value above the usual 35U/ml cutoff, returning to normal after delivery. obesity and extra adipose tissue also boost the level, while smoking, caffeine and certain surgeries tend to lower it. Conditions like heart failure, cirrhosis or ascites raise the marker, whereas osteoporosis or coronary artery disease are linked to lower readings. Elevated values are not specific to ovarian malignancy; they also rise in lung and breast cancers. [15][Figure 1]

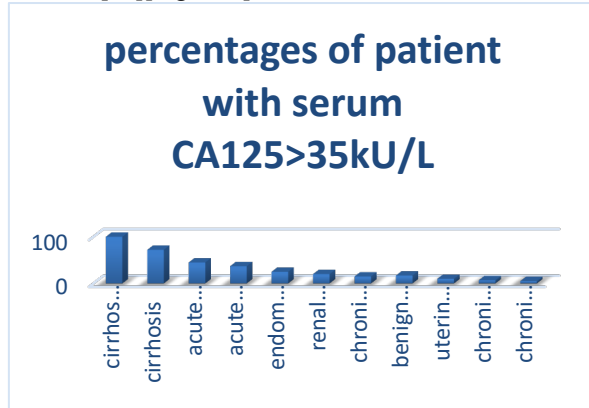


Fig 1: Non-Malignant Conditions Causing Elevated CA125 Concentrations

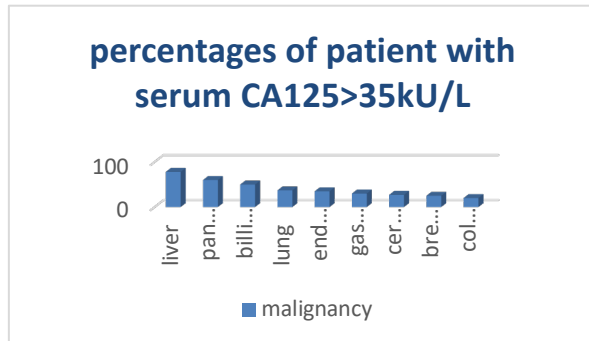


Fig 2: Frequency of Elevated CA 125 Concentrations In Different Malignancies

3. Ovarian Cancer

3.1 Prognosis And Survival Rate

Advanced ovarian cancer has a <20% 10year survival rate despite surgery and chemotherapy. Primary debulking surgery (complete tumor removal with no visible residual disease) is the preferred first treatment. Patients with stage IIIC/IV disease who achieve optimal debulking (no residual disease) have a significantly higher 7 year survival rate than those having any residual disease (73.6% vs. 21%). Stage IIIa/b patients are more likely than IIIC/d patients to get optimal resection. Optimal debulking followed by chemotherapy reduces remaining cancer cells and improves survival. Prognosis depends on tumor location, size, mutation status and surgical skill(not just stage or diagnosis timing). Recurrent OC usually

has a 12-24 month median survival and is often considered incurable; <30% survive for 5years and <5% survive for 12years. Residual diseases after primary surgery raises recurrence risk sharply. Overall cancer survival has risen due to better screening, surgery and treatments. Chemotherapy has only modestly- improved 12 year survival for advanced disease. Monitoring with exams, imaging and CA125 can detect recurrence; 80-90% of recurrences are preventable with early detection. [16]

CA125 functions as both a diagnostic indicator and a therapeutic response gauge for ovarian malignancies. Traditional detection relied on physical exams and imaging, but these methods proved insufficient for substantial pelvic tumors. Changes in the level of CA 125 forecast disease progression or regression about 90% of the time. Elevations above 35U/ml threshold signal relapses after first-line therapy with 62-94% sensitivity and 91-100% specificity.

3.2 Types and Stages of Ovarian Cancer

Ovarian neoplasms are classified into type-I and type-II, each with distinct developmental and prognostic traits. Borderline lesions evolved into type-I lesions, which advance through stages-I and II. Type-I precursors are easy to locate, where as type-II precursors are elusive. Most type-II tumors, such as serous tubal intraepithelial carcinomas (STIC), arise in fallopian tubes and typically present at advanced stages (III-IV). They differ morphologically and genetically from type-I lesions. Early identification of stage-I diseases was once viewed as a key prognostic factor but many aggressive high-grade serous carcinomas (type-II) are detected only after peritoneal invasion. Focusing on early stage detection has limited survival impact as type-I cases dominate diagnosis, creating a 'crisis of confidence' amid stagnant survival rates. Consequently, reduced mortality from early stage disease seems linked more to biological differences between the two subtypes than to stage distribution at diagnosis. Some groups now advocate screening aimed at spotting low-volume type-II cancers when cytoreductive surgery can achieve complete resection. [17]

Developing effective biomarkers requires understanding OC subtypes, which have variable CA125 expression. HGSC and endometrioid tumors express CA125 strongly; serous tumors have higher CA125 than mucinous tumors. Type-I cancers are younger, often asymptomatic early stage; type-II cancers have higher CA125, cause 90% of mortality and 75% of carcinomas. It has the strongest discriminating power for type-II tumors vs. healthy controls. Type-II tumors show abrupt serum CA125 changes vs. type-I. A multicenter trial on stage III/IV patients found CA125>500U/ml linked to poor

cytoreduction (>1 cm residual cancer). [18][[TABLE 2]

	Type-I	Type-II
subtypes	Endometrioid, clear cell, low-grade serous carcinomas (LGSC), mucinous carcinomas, seromucous carcinomas, malignant Brenner tumours	High-grade serous carcinoma (HGSC), carcinosarcoma, undifferentiated carcinoma
Genetic stability	Genetically stable	Genetically unstable
Diagnosis	early stage	Advanced stage
Early detection	frequent	Infrequent
Progression	slow	Rapid
TP53 mutations	infrequent	Frequent
Germline BRCA mutations	infrequent	Frequent
Ki 67 proliferative index	10-15%	50-75%
Median CA125 levels	53-413 U/ml	395-1340U/ml

Table 2 type I versus type II carcinomas

4. Materials and Methods

4.1 Materials

4.1.1 Ethical statement

Under the supervision of Dr. Biswajit Pradhan, an assistant professor of biochemistry, this endeavor was given permission to proceed by Acharya Harihar Post Graduation Institute of Cancer in Cuttack. All the information were gathered from the data sheet of onychopathology department. Before taking blood samples from patients, individual consent was obtained. The data sheet of around 10,000 women who came for testing served as the source of the information for this research.

4.1.2 Data source and participants

This cohort study used connected data from Acharya Harihar post Graduate Institute of Cancer's registered data sheet. It contains anonymous primary care data on 10,000 patients (demographics, test findings, symptoms and diagnosis). Data includes tumor topography, stage and diagnostic date. Women with a CA125 measurement in primary care between 1st

January to 30th June 2023 were included and the test was done for a potential ovarian cancer symptom.

4.1.3 Sample collection

From January-june 2023, serum samples were collected from 347 patients at AHPGIC, Cuttack. Inclusion criterion; histopathological confirmed malignant tumors.

The NC group had no tumor history.

Exclusion criteria

- Blood system disorders, thrombosis or hemorrhagic disease
- Use of antibiotics, anti-coagulants, hormones or nitrogen-containing meds
- Significant pre-admission blood loss affecting tests

143 patients were split into 2 groups

- OC group (n=55; 39 serous OC, 10 ovarian adenocarcinomas, 1 clear-cell carcinoma, 3 mucinous ovarian carcinomas, 2 endometrioid ovarian carcinoma)
- Non-OC group (n=88) with other malignancies (lung, gastric, colon, liver and rectal cancers)

The above study was ethics-approved and all patients gave informed consent.

4.1.4 Quality Assessment, Search Strategy And Selection Criteria

We conducted cohort studies to identify every publication on the association between blood CA125 levels and ovarian-cancer survival. Search terms like (survival/ mortality prognosis in ovarian cancer) considered as an outcome were combined with CA125 related terms (pre/post operative/ chemotherapy serum CA125, half-life, nadir level and AUC) as a predictor. Accepted designs case control, cohort, cross-sectional, prospective, retrospective, case series, longitudinal, clinical trial, meta-analysis. No restrictions on age, ethnicity or cancer stage.

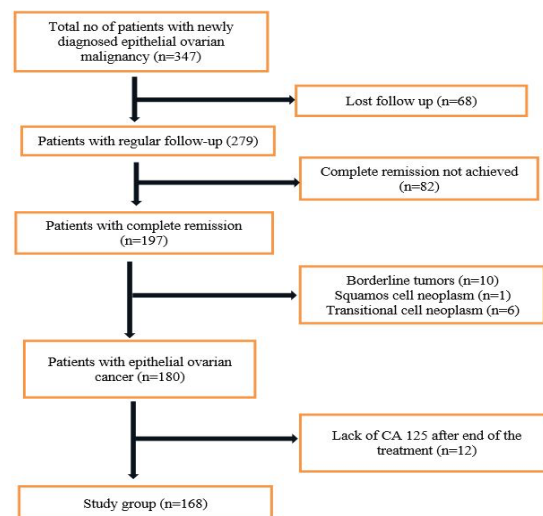


Fig 3: Qualification scheme of patients for the study

4.1.5 Statistical analysis-

The study evaluated CA125 for OC by calculating PPV, NPV, sensitivity, specificity and AUC of the ROC curve. The analysis was done for all cancers and repeated after excluding OC cases. All tests were restricted to women above 50 years because OC incidence rises on post-menopausal women. The regression model predicted cancer odds for CA125 levels 1-1000U/ml, converting odds to probabilities. For women above 50, significant age related differences in predicted probabilities led to a multivariable model using CA125 and age with the same spline method. This model estimated OC for women aged 30-80 with CA125 1-1000U/ml.

4.2 Methodology

4.2.1 Introduction-

CA125 marker has poor sensitivity and specificity in early stages when measured by antibody-based immunoassays. Mass spectrometry shows CA125 exists as various molecular-weight isoforms that haven't been verified, affecting test reliability. Western blot identified CA125; positive results up to 500 kDa likely come from interactions between M11 and OC125 like antibodies. Mass spectrometry and 2D gel electrophoresis revealed fibronectin causes false-positive CA125 readings in 1st generation ELISA, suggesting antibody cross-reactivity with other proteins. [19][20]

Basic elements were

- Coating/capture- immobilize antigens (direct or indirect) on polystyrene microplate wells
- Plate blocking- add irrelevant protein to cover unsaturated surface sites
- Probing/detection- incubate with antigen-specific antibodies that affinity-bind
- Measurement- detect signal from direct or secondary tag on the antibody

4.2.2 Procedure

Materials Required- Clear 96 well plate, Multi-channel precision pipettor with disposable plastic tips, Plate reader or luminometer equipped to detect the substrate. [Table 3]

reagents	
Coating buffer	0.2M sodium carbonate/bicarbonate, pH 9.4
Capture antibody	Diluted in coating buffer (see appendix for appropriate concentration range)
Wash buffer	M phosphate, 0.15 M sodium chloride, pH 7.2 containing 0.05% Tween20

	(0.1M phosphate can be replaced by 25mM Tris, pH 7.2)
Blocking buffer	2% (w/v) bovine serum albumin (BSA) in wash buffer
Standard diluents	2% (w/v) BSA in wash buffer. (ideally the standard diluent composition would be as close as possible to the sample matrix. For example, if measuring the concentration of an antigen in culture supernatant, culture medium should be used as the standard diluent. However biological sample matrices such as serum are impossible to replicate, therefore BSA is commonly used in these instances. Often the blocking buffer is also used as the standard diluent.
Samples/standards	Mentioned in the preparation section
Detection antibody(biotinylated)	Diluted in 1/5 strength standard diluent (see appendix for appropriate concentration range)
Enzyme conjugate	Streptavidin-HRP diluted in 1/5 strength standard diluent
substrate	TMB substrate
Stop solution	2M sulfuric acid

Table 3: Reagents used for testing of samples
ELISA Procedure

- Standards: make a standard curve (0-1000 pg/ml, can go to 3000pg/ml). prepare 2 or 3-fold serial dilutions of the stock with standard diluent; use fresh tips each step.
- Samples: if antigen > 1000 pg/ml, dilute the sample with standard diluent to bring it into the curve range.
- Procedure:
 - Do not let the plate dry.
 - Dilute capture antibody to 50-100 microliter/well. Add, cover and incubate 2h RT.

- Wash 3×5 min with 200 microliter wash buffer (shaking)
 - Add 300 microliter blocking buffer, incubate 1h RT (or overnight 4⁰c)
 - Remove block, add samples/standards (same volume as capture Ab), and incubate 1h RT.
 - Wash 3×5 min with 200 microliter wash buffer
- Detection antibody: Dilute biotinylated Ab to the same volume as capture Ab. Add, incubate at 1h RT. Wash 3×5 min with 200 microliter wash buffer
 - Enzyme conjugate- dilute to the same volume as capture Ab, Add, incubate at 1h RT. Wash 6×5 min with 200 microliter wash buffer
 - Substrate: Add substrate (same volume as capture Ab). Incubate RT until desired color develops.
 - Stop and read: Add equal volume of stop solution. Measure absorbance at 450nm (for TMB) or use appropriate detection for other substrates. [21]

5. Results and Discussion

5.1 Clinical outcomes

5.1.1 Primary outcome

The main clinical result was detection of ovarian cancer 6months after the original CA125 test (AHPGIC data). Ovarian cancer was classified using FIGO & WHO codes (C56, C57.0, C48.1, C48.2 or D39.1). We assumed cancer existed at the time of the CA125 test if it was found with in a year of the original test. A 1-year window was chosen to balance incidental cancers and relevant malignancies. Borderline ovarian tumors were included per NICE CA125 guidelines; they are managed like invasive tumors and have good prognosis even when discovered later.

5.1.2 Secondary outcome

It was detection of non-ovarian malignancies (excluding non-melanoma skin tumors) in women without ovarian cancer 6months after initial CA125 testing. These are called 'non-ovarian cancer'; together with ovarian cancer they are termed 'all cancers'.

5.1.3 Descriptive outcomes

A NICE-based symptom code list identified complaints in the 30days before testing to report symptoms that may have prompted the test. Ovarian cancer stages were determined using the TNM or FIGO staging systems.

5.2 Results

Our cohort had 50,780 women after exclusions. The incidence of ovarian cancer in the cohort was 0.9%,

and it was three times higher in the 50+ group than other groups. The mean patient age was 56 years (interquartile range: 18– 102 years), and the median time between CA125 testing and ovarian cancer diagnosis was 42 days (interquartile range: 25–62 days).

5.2.1 Cancer stages

Out of the 456 ovarian cancers, 172 (37.7%) were stage I or II, and 209 (45.8%) were stage III or

IV. No stage was recorded in 75 (16.4%) cases. [Table 4]

Table 4 Patient numbers, incidence of raised CA 125 tests and cancer incidence by age group

5.3 Cancer Morphology and Histology

21.5%(n=98) of OC were borderline tumors. It was 50% of malignancies in <50 year patients vs. 15.4% in >50 year patients. Serous epithelial tumors were the most common type, making up 48.6% (n=174) of invasive tumors. Invasive non-epithelial tumors were 12.5% (n=5) in <50 year patients vs. 2.5% (n=8) in >50 year patients.

cancer	group	PPV, % (95% CI)	NPV, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	AUC (95% CI)
Ovarian	All ages	10.1 (9.1-11.2)	99.8 (99.7-99.8)	77.0(72.8-80.8)	93.8(93.6-94.0)	0.92(0.90-0.93)
	<50 year	3.4(2.5-	99.8(99.8-	62.5(51.0-	92.7(92.3-	0.86(0.82-

	s	4.4)	99.9)	73.1)	93.1)	0.91)
	>50 year s	15.2(13.6- 16.8)	99.7(99.7- 99.8)	80.1(75.7- 84.0)	94.5(94.3- 94.8)	0.93(0.92- 0.96)
Ova rian; inva sive	All ages	8.8(7 .8- 9.8)	99.9(99.9- 99.9)	84.9(80.8- 88.5)	93.7(93.5- 93.9)	0.94(0.92- 0.96)
	<50 year s	2.0(1 .3- 2.8)	99.9(99.9- 100)	72.5(56.1- 85.4)	92.6(92.2- 93.0)	0.88(0.82- 0.95)
	>50 year s	13.8(12.4- 15.4)	99.9(99.8- 99.9)	86.5(82.2- 90.0)	94.4(94.2- 94.7)	0.95(0.93- 0.97)
Non - ovar ian	All ages	12.3(11.2- 13.5)	98.0(97.9- 98.1)	29.1(26.6- 31.6)	94.4(94.2- 94.6)	0.68(0.66- 0.69)
	<50 year s	2.8(2 .0- 3.8)	99.3(99.2- 99.4)	24.8(18.4- 32.3)	92.8(92.5- 93.2)	0.62(0.58- 0.67)
	>50 year s	20.4(18.5- 22.4)	97.2(97.0- 97.4)	29.7(27.0- 32.4)	95.5(95.2- 95.7)	0.70(0.69- 0.72)
All canc ers	All ages	21.2(19.8- 22.6)	97.8(97.7- 97.9)	41.4(39.1- 43.7)	94.4(94.2- 94.6)	0.74(0.73- 0.75)
	<50 year s	6.1(4 .9- 7.4)	99.2(99.0- 99.3)	37.3(31.2- 43.8)	92.8(92.5- 93.2)	0.70(0.67- 0.74)
	>50 year s	32.5(30.4- 34.6)	96.9(96.7- 97.1)	42.0(39.5- 44.5)	95.5(95.2- 95.7)	0.76(0.75- 0.78)

Table 5: Performance Characteristic of CA125 for the Above Cancers.

5.4 Recorded Symptoms

Symptoms of possible ovarian cancer were recorded for 24,269 women (47.8%) on the same day or in the 30 days preceding CA125 testing; the most common was abdominal pain. Multiple symptoms were recorded in 1,477 (6.1%) women. [Table 6]

Symptom/sign	Patients, N(%)
Abdominal pain	11,933 (49.2)
Abdominal distention or bloating	5686(23.4)
Change in bowel habit	2866 (11.8)
Fatigue	1692 (7.0)
Pelvic pain	1632 (6.7)
Weight loss	913 (38)

Urinary frequency	552 (2.3)
Abdominal or pelvic mass	419 (1.7)
Loss of appetite	113(0.5)
Urinary urgency	863(0.4)
Ascites	26 (0.1)

Table 6: Ovarian cancer symptoms and signs coded in the 30 days prior to CA125 testing. % is the proportion of patients with a given symptom out of the total number of patients who have a coded symptom (N = 11,933). Categories are not mutually exclusive: a patient may have had more than 1 symptom coded.

5.5 Diagnostic performance applying the standard cutoff

The diagnostic performance of CA125 using a >35U/ml cut of shows

PPV-10.1% (OC); 8.8% for invasive OV

NPV- 99.8%

Sensitivity- 77.0% (overall); 84.9% for invasive OC

Specificity- 93.8%

AUC- 0.92

AUC, PPV, sensitivity and specificity are higher in the >50-years group. In women with CA125>35U/ml, the PPV for non-ovarian cancers is 12.3%; with CA125<35U/ml, it is 2.0% . [Table 7]

Cancer type (ICD10 codes)	N	N< 35 U/ml(%)	N>35 U/ml(%)
Unknown primary(C80)	46	8(7)	38(83)
Secondary; respiratory and digestive (C78)	23	9 (39)	14 (61)
Pancreas (C25)	93	47(51)	46(49)
Lung(C34)	10 4	55(53)	49(47)
Liver, biliary (C23,C22,C24)	34	21(62)	13(38)
Uterus(C54,C55,D39)	13 2	84(64)	48(36)
Upper GI (C15,C16,C17,D37.1, D37.2)	66	46(70)	20(30)
Lower GI (C18,C19,C20,C21,D37.3,D37 .4,D37.5)	25 5	197(7 7)	58(23)
Haematological(C81,C82,C83, C84,C85,C90, C91,C92,C96,D45,D46,D47)	11 2	83(74)	29(26)
Kidneys, urinary tract	78	65(83)	13(17)

(C64,C65,C66, C67,D41)		)	)
Breast (C50)	15 4	142(9 2)	12(8)
others	22 4	180(8 0)	44(20)
total	13 21	937(7 1)	384(2 9)

Table 7: Cancers diagnosed in women without ovarian cancer

6. Conclusion

The study of 10,000 women who got CA125 tests found-

- 10.1% of those with CA125>35 U/ml were diagnosed with OC; 12.3% got another cancer diagnosis
- About a third of women>50 years with CA125>35U/ml had some cancer
- The overall risk of OC equals a CA125 of 53U/ml
- Women> 70 years had a 3% chance of lower CA125 levels compared with younger or older women

In primary care, it helps detect OC, especially in women above 50. Clinicians should also consider non-ovarian cancers after ruling out OC, because elevated CA125 and age raise the overall cancer likelihood.

6.1 Study Limitation Includes

- Data issue- the rationale for CA125 requests couldn't be pinpointed because symptoms are recorded in free text and aren't always classifiable, which may introduce bias.
- Omitted factors- variables like ethnicity or smoking that affects CA125 were left out to keep the model simple for general practice.
- Accuracy problem- stage-specific CA125 accuracy wasn't assessed because cancers often progress in the 12months before diagnosis and tests were taken at varying intervals.
- Modeling caution- restricted cubic splines were used for the age-CA125-cancer relationship, results for extreme ages or very low CA125 should be treated with caution.

6.2 Discussions

Epithelial OC is common in Scandinavia, western Europe and North-America, with <40% 5-year survival. CA125 is the most used serum tumor marker for early detection and prognosis. It guides treatment tailoring and monitors response to therapy, relapse and progression. High pre-operative CA125 often indicates

advanced diseases. Post-therapy CA125 changes reflect tumor mass; its half-life (t1/2) and doubling time are kinetic parameters for follow-up.

At1/2 of 20 days predicts treatment response and survival. Though CA125 assays are routine during chemotherapy, its prognostic Value alone is limited. Rising CA125 signals recurrence and poor survival; falling levels suggest good response. Future research should focus on longitudinal studies of CA125 and survival.

6.3 Conclusion

OC is a heterogeneous disease with varying subtypes and prognosis. Type-I cancers are usually detected early and have a good long-term outlook, while aggressive type-II cancers are found late and have a poor survival prognosis. CA125 has been used for decades in screening, treatment and follow-up of OC, improving survival for both tumor types when detected early. However, early detection of stages-I & II remains limited. A new paradigm focuses on low volume type-II cancers, requiring accessible and affordable screening to diagnose type-II tumors early. Point-of-care (POC) CA125 assays with higher cut-offs and longitudinal monitoring may be more useful than a single threshold, especially for early sub stages (IIIa/b) where optimal cyto-reduction is possible. POC readings can also identify advanced type-II cancers. CA125 sensitivity can be enhanced by combining it with other biomarkers. Consequently, current CA125-based screening methods need review to achieve significant reductions in ovarian cancer mortality.

7. References

1. 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;309:883Y887
2. Zohre M, Azita T, Safoura T, et al. Ovarian cancer in the world: epidemiology and risk factors. *Int J Womens Health.* 2019 30;11:287–299.
3. Tamakoshi K, Kikkawa F, Hasegawa N, et al. Clinical value of a new serum tumor marker, CA125II, in gynecologic disease: comparison with CA125. *GynecolObstet Invest* 1995;39:125–129.
4. Tanmay G, Muhammad Z, Harshil B. Cancer Antigen 125.2025 jan
5. Parsa C, Cezary C, Jacek G. et al. CA125 and Ovarian Cancer: A Comprehensive Review. *Cancers (Basel).*2020 12(12):3730.
6. Papsidero LD, Wang MC, Valenzuela LA, Murphy GP, Chu TM. A prostate antigen in sera of prostatic cancer patients. *Cancer Res* 1980;40:2428–2432. [PubMed: 7388802.

7. Rao AR, Motiwala HG, Karim OM. The discovery of prostate-specific antigen. *BJU Int.* 2007.
8. <https://my.clevelandclinic.org/health/diagnostics/17830-ca-125-blood-test>.
9. Vincent D, Hélène C, Edouard V, et al. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. *J Ovarian Res.* 2019 Mar 27;12:28.
10. Rapkiewicz AV, Espina V, Petricoin EF III, Liotta LA: Biomarkers of ovarian tumours. *Eur J Cancer* 2004, 40:2604-2612.
11. Minting X, Rong L, Anqi Z et al. Developments in ovarian cancer markers and algorithms. *European Journal of Gynaco and Onco.* Vol.46, Issue 6, June 2025 pp.14-22.
12. Tuxen MK, Soletormos G, Dombernowsky P: Tumor markers in the management of patients with ovarian cancer. *Cancer Treat Rev* 1995, 21:215-245.
13. John R, John T et al. Transvaginal ultrasonography in ovarian cancer screening: current perspectives. *Int J Womens Health.* 2013 Dec 20;6:25–33.
14. Malte R, Michael F, Jonathan S, et al. Cancer of the ovary, fallopian tube, and peritoneum: 2025 update. 04 September 2025.
15. Alamtaj S, Alireza F, Marjan H, et al. Factors influencing serum concentration of CA125 and CA15-3 in Iranian healthy postmenopausal women, *Pathol Oncol Res.* 2007;13(4):360
16. Masafumi K, Noriomi M, Ikuo K et al. Recent Concepts of Ovarian Carcinogenesis: Type I and Type II. *Biomed Res Int.* 2014 Apr 23;2014:934261.
17. Jacobs IJ, Skates SJ, MacDonald N, Menon U, Rosenthal AN, Davies AP, Woolas R, Jeyarajah AR, Sibley K, Lowe DG, Oram DH: Screening for ovarian cancer: a pilot randomised controlled trial. *Lancet* 1999, 353:1207-1210.
18. Rapkiewicz AV, Espina V, Petricoin EF III, Liotta LA: Biomarkers of ovarian tumours. *Eur J Cancer* 2004, 40:2604-2612.
19. Tuxen MK, Soletormos G, Dombernowsky P: Tumor markers in the management of patients with ovarian cancer. *Cancer Treat Rev* 1995, 21:215-245.
20. Feng C, Yi L, Chunyan C et al. Respective and simultaneous detection tumor markers CA125 and STIP1 using aptamer-based fluorescent and RLS sensors. *Sensors and Actuators B: Chemical.* Volume 245, June 2017, Pages 470-476.
21. Feeley KM, Wells M. Precursor lesions of ovarian epithelial malignancy. *Histopathology* 2001;38:87– 95.