



ISSN (P): 2617-7226
ISSN (E): 2617-7234
www.patholjournal.com
2021; 4(3): 158-161
Received: 16-06-2021
Accepted: 18-07-2021

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CA-125: A potential screening tool for benign and malignant lesions in post-menopausal females presenting with adnexal mass at a tertiary care center in Saurashtra region

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DOI: <https://doi.org/10.33545/pathol.2021.v4.i3c.408>

Abstract

Background: Among women ovarian cancer the seventh-most common cancer and the eighth-most common cause of death from cancer. The typical age of diagnosis is 63. When this process begins, there may be no or only vague symptoms. Symptoms become more noticeable as the cancer progresses. With the increasing load of patients in our setup it is essential to look for serum tumor markers which can help narrow down patients who require attention. CA-125 is the most frequently used biomarker for ovarian cancer detection. Not only CA-125 helps to screen patients in certain age group but also monitor therapy. This study aims to find out the use of CA-125 as a potential tool for screening ovarian cancer in certain age groups in conjunction with other findings.

Materials and Method: This is a retrospective study which entails assessment of serum CA-125 level in post-menopausal females (>45 years old female considered in this study) who presented with a history of adnexal mass.

Result: CA-125 has a sensitivity of 90.55% and specificity of 74.28% in detecting ovarian malignancies in post-menopausal females.

Conclusion: Within the paradigm of this study CA-125 serves as a good marker for screening of post-menopausal females who present with adnexal mass and it is best used in conjunction clinical findings and with other diagnostic modalities like ultrasonography.

Keywords: ovarian tumor, CA 125, screening

Introduction

Ovarian cancer is the leading cause of mortality from gynecologic cancers in the United States (US), resulting in approximately 14,500 deaths annually [1]. When this process begins, there may be no or only vague symptoms [2]. Symptoms become more noticeable as the cancer progresses [2].

The risk of ovarian cancer increases in women who have ovulated more over their lifetime. This includes those who have never had children, those who begin ovulation at a younger age and those who reach menopause at an older age [3]. Other risk factors include hormone therapy after menopause, fertility medication, and obesity [4, 5]. Factors that decrease risk include hormonal birth control, tubal ligation, and breast feeding [5]. A blood test for a marker molecule called CA-125 is useful in differential diagnosis and in follow up of the disease, but it by itself has not been shown to be an effective method to screen for early-stage ovarian cancer due to its unacceptable low sensitivity and specificity [6]. CA-125 levels in premenopausal people over 200 U/mL may indicate ovarian cancer, as may any elevation in CA-125 above 35 U/mL in post-menopausal people. CA-125 (cancer antigen 125, carcinoma antigen 125, or carbohydrate antigen 125) also known as mucin 16 or MUC16 is a protein that in humans is encoded by the MUC16 gene [7]. The most widely used tumor marker in ovarian cancer, often considered the 'gold standard' is CA125 [8]. It was first identified by Bast, Knapp, and colleagues [9] in 1981. CA125 is a high molecular weight glycoprotein which is raised in approximately 90% of patients with advanced epithelial ovarian cancer [10]. CA 125 is expressed by fetal amniotic and coelomic epithelium and in adult tissues derived from the coelomic (mesothelial cells of the pleura, pericardium, and peritoneum) and Mullerian (tubal, endometrial, and endocervical) epithelia.

The CA 125 test only returns a true positive result for about 50% Stage I ovarian cancer patients. The CA 125 is not an adequate early detection tool when used alone. The CA 125 test has an 80% chance of returning true positive results from Stage II, III and IV ovarian cancer patients. The other 20% of ovarian cancer patients do not show any increase in CA 125 concentrations. However, several female reproductive disorders can cause a false positive result. Endometriosis, Benign Ovarian cysts, first trimester of pregnancy, and pelvic inflammatory diseases all produce higher levels of CA 125. 70% of people with cirrhosis, 60% of people with pancreatic cancer and 20-25% of people with other malignancies have elevated levels of CA 125. The CA 125 test should not be used alone to detect ovarian cancer, but rather with transvaginal sonography and rectovaginal pelvic examination for greater accuracy. CA 125 can be used to distinguish malignant from benign pelvic masses. Even in post-menopausal patients most pelvic masses are found to be benign; nevertheless, surgical exploration is still often required to rule out malignancy. Among post-menopausal patients with a pelvic mass, a CA 125 level greater than 65 U/mL has distinguished malignant disease with greater than 90% accuracy. As ovarian cancers can be found in the presence of a normal CA 125 a value less than 35 U/mL should never discourage surgical exploration of a post-menopausal patient with a suspicious adnexal mass. The positive predictive value of CA 125 in women with an adnexal mass is 35% to 91%, and the negative predictive value ranges between 67% and 90% [11]. The sensitivity of CA 125 in distinguishing between benign and malignant masses ranges between 61% and 90%, while specificity

ranges between 35% and 91% [11].

Aims and Objective

The study aims to find out the sensitivity, specificity, positive predictive value and negative predictive value of CA-125 in post-menopausal females presenting with adnexal masses. The study focuses to evaluate CA-125 either as an independent marker or in correlation with other investigations to evaluate post-menopausal females for adnexal mass and classify as benign or malignant lesion.

Methodology: In this study, which is of retrospective design, post-menopausal females (>45 years) presenting with adnexal mass were segregated. Blood sample 2 ml was drawn by venipuncture and collected in plain (Clot activator) vacuette. Serum was separated from the sample and was used to assess CA-125 level. CA-125 level was estimated using semi- automatic ELISA based solid phase enzyme immunoassay for the quantitative determination (Kit by calbiotech). All the values were determined on Readwell Touch Semi-automatic ELISA reader.

Study Duration: This retrospective study spanned over a period of two years (November 2017 to Dec 2019) and the study was conducted at the Pathology Department at M.P. Shah Medical College and G.G. Hospital, Jamnagar.

Sample size: All the post- menopausal females with adnexal masses (88) who reported at the gynecology department at M.P. Shah Government Medical College and G.G. Hospital in the study duration were evaluated.

Table 1: Age wise incidence of all the cases with CA 125 values and cases in which the ultrasonography suggested of neoplasm.

Age (in years)	Number of patients	CA 125				Adnexal Mass s/o neoplasm on USG
		Normal Values & Benign on workup	High Values & Malignant on workup	High Values & Benign on workup	Low Values & Malignant on workup	
40 – 44	1	0	1	0	0	1
45 – 49	27	8	12	4	2	13
50 – 54	16	2	11	3	1	13
55 – 59	6	2	4	0	0	2
60 – 64	18	7	9	1	1	8
65 – 69	4	0	3	0	1	3
≥70	16	7	8	1	0	7
Total	88	26	48	9	5	47

Observation: In our study we had 88 post-menopausal females presented with history of adnexal mass of variable sizes. Out of these 88 cases, 47 females had adnexal masses with sonographic findings suggestive of neoplastic origin or had strong clinical suspicion of malignant mass and correlated history. 26 females presented with adnexal mass with no evidence of malignancy on sonography. On assessment with CA-125 out of 88 females, 48 female patients had significant elevation of CA-125, i.e. over 35 U/mL. 31 patients had low values < 35 U/mL. Sensitivity of CA-125 came out to be 90.56% and specificity came out to

be 74.28%. Positive predictive value came out to be 84.21% and negative predictive value came out to be 83.87%. Out of all these cases 37 cases were followed up with histopathological examination and were confirmed as epithelial ovarian malignancies. These patients were followed up with serial CA 125 levels over course the of their chemotherapy treatment. These patients showed a decreasing trend of CA-125 levels. A sensitivity of 88.09 % was found in these histopathologically proven cases, serving as an internal control to this study.

Table 2: Comparison of sensitivity, specificity, positive predictive value and negative predictive value in various studies.

Study and value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
C. A. Hartman <i>et al.</i> 13 (on USG)	67%	80%	75	73
C. A. Hartman <i>et al.</i> 13 (CA 125)	69	87.8	69	88
Grzybowski W <i>et al.</i> 14 (CA 125)	88.73	98.07	98.44	86.44
EL Moss <i>et al.</i> 12	88.6	72.0	--	--
Present study (USG)	94	81	82.4	91.1
Timmerman <i>et al.</i> 16	93	90		
Present Study (CA 125 HPE proven)	88.09	65	74	83.8
Present Study (CA 125)	90.56	74.28	84.21	83.87

Timmerman *et al.* 16 - Five simple rules to predict malignancy (M-rules): (1) irregular solid tumor; (2) ascites; (3) at least four papillary structures; (4) irregular multilocular-solid tumor with a largest diameter of at least 100 mm; and (5) very high color content on color Doppler examination. We chose five simple rules to suggest a benign tumor (B-rules): (1) unilocular cyst; (2) presence of solid components where the largest solid component is < 7 mm in largest diameter; (3) acoustic shadows; (4) smooth multilocular tumor less than 100 mm in largest diameter; and (5) no detectable blood flow on Doppler examination.

Discussion

Within the paradigm of this study we found that CA 125 has a specificity of 74.28%, sensitivity of 90.56% in females with adnexal masses who had strong clinical suspicion and/or USG suggesting ovarian carcinomas. Compared to the study conducted by C. A. Hartman *et al.* [13] where Specificity was 87.8% and sensitivity was 69% and in study conducted by EL Moss *et al.* [12] it was 72.0% and 88.6% respectively and similarly in the study conducted by Grzybowski W *et al.* [14] it was 98.07% and 88.73% respectively. A mean CA 125 value of 194.93 U/mL was found in females who aged >50 years (60 cases). For the entire study mean age was found to be 56.50 years and mean CA 125 value was 184.22 U/mL.

As internal control for this study out of the 48 cases we screened with high CA 125 values we followed up 37 cases with histopathological examination (Suggestive of Ovarian Epithelial malignancies) and we found comparable values of sensitivity and specificity 88.09% and 65 % respectively. Also, these histopathologically proven cases when came for serial follow up of CA 125 post chemotherapy showed a decreasing trend in their CA 125 values.

We also found the sensitivity and specificity of USG in detecting ovarian malignancies and we found the sensitivity to be 94% and specificity of 81% compared to 67% and 80 % respectively in study conducted by C. A. Hartman *et al.* [13].

Conclusion

CA-125 can be used as a good predictive marker to assess post-menopausal females with adnexal mass and can be used to differentiate between benign and malignant origin of masses. CA 125 serves as a good marker to diagnose advanced malignancies (Stage III and IV) but however some Stage I malignancies may be missed. However, CA 125 can be utilized as a marker to screen patients when it is used for serial monitoring rather than just a single point value. CA 125 also gives a high value in conditions like endometriosis which need to be meticulously ruled out. In our study a good sensitivity of 90.56% and specificity of 74.28% was found so it can be used reliably to help triage patients according to their condition. CA 125 in its versatility with its use in ROMA and RMI score, low cost per test and serial values as a screening test outweighs more specific, HE 4 and OVA 1. However, CA 125 should not be used as a standalone marker for such cases and correlation with sonographic evidence and clinical examination is always advised.

Acknowledgement

The samples for this study were acquired with the help of Dr. Nita Rada, Assistant Professor, Department of Obstetrics and gynecology, M.P. Shah Medical College and G.G. Hospital Jamnagar.

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