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**Original Research Article**

# Pseudocholinesterase, aspartate transaminase, alanine transaminase as markers for cervical cancer: a study in a tertiary care hospital

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## ABSTRACT

**Background:** Cervical cancer is a malignant neoplasm arising from cells originating in the cervix, almost always caused by human papillomavirus (HPV). Butyrylcholinesterase is a non-specific cholinesterase enzyme that hydrolyses different choline esters. PCHE levels were lower than the normal at all the stages of cancer cervix. The present study was attempted to find out the role of some of the biochemical markers like serum pseudocholinesterase (PCHE), serum aspartate transaminase (AST), and serum alanine transaminase (ALT), in malignancy of the uterine cervix.
**Methods:** 60 patients aged between 30 -70 years who were having cervical cancer were included into the study and 30 healthy patients within the same age group were included as controls. 5ml of venous blood was collected from all the study participants under aseptic conditions in a plain tube. Serum Pseudocholinesterase, Serum Aspartate transaminase and Serum Alanine transaminase was estimated for all the patients in both the groups.
**Results:** The mean value of pseudocholinesterase in cervical cancer patients was lower in the cases when compared to controls and it was statistically significant (P value 0.0005), while the mean value of serum AST and ALT were higher in cases when compared to controls and it were also statistically significant. When compared with Pearson's coefficient, the serum PChE had a significant negative correlation with AST and ALT, while the serum AST had a significant positive correlation with ALT and a negative correlation with PChE.
**Conclusions:** Among the women with cervical cancer, it was observed that the enzyme activity of PChE was lower than normal, while that of SGPT and SGOT were higher. PCHE, AST, and ALT can be used as tumor markers in the management of malignancy of the uterine cervix.

**Keywords:** Cervical cancer, Serum aspartate transaminase, Serum alanine transaminase, Serum pseudocholinesterase

## INTRODUCTION

Cervical cancer is a malignant neoplasm arising from cells originating in the cervix. It is usually a slow-growing cancer that may not have symptoms but can be found with regular Pap tests. Cervical cancer is almost always caused by human papillomavirus (HPV) infection.[1] Cervical cancer is reported to be the second most common and the fifth deadliest cancer in women in the world.[2,3] In 2008, it was estimated that there were 473,000 cases of cervical cancer, with approximately 80% occuring in developing countries.[4] In 2012, in India, about 122,844 new cervical cancer cases were diagnosed annually, resulting in 67,477 deaths. It was found to be the 2nd leading cause of cancer deaths in women aged 15 to 44 years in India.[5]

Butyrylcholinesterase which is also known as pseudocholinesterase, plasma cholinesterase, BCHE or BuChE, is a non-specific cholinesterase enzyme that hydrolyses different choline esters. Primarily found in the liver, it is very similar to the neuronal

acetylcholinesterase, which is also known as RBC or erythrocyte cholinesterase. Assay of butyrylcholinesterase activity in plasma can be used as a liver function test as both hypercholinesterasemia and hypocholinesterasemia indicate pathological processes.[6] PCHE levels were lower than the normal at all the stages of cancer cervix.[7] In cancer, with or without liver impairment, serum BChE levels serve as an accurate functional and prognostic indicator, useful for monitoring clinical and therapeutic interventions according to patients' prognosis. Its serum level decreases in many clinical conditions such as acute and chronic liver damage, inflammation, injury, infections, and malnutrition.[8]

BChE levels are strongly influenced by inflammation, sensitively decreasing in the acute inflammatory phase and promptly increasing when inflammation improves.[9] BChE is a valid prognostic indicator, strictly related with nutritional status and inflammation.[8] Advanced cancer is a condition in which mild to moderate inflammation is frequent and interacts with various degree of PEM. Plasma BChE levels resulted to be decreased in advanced cancer patients, with or without hepatic involvement: the lowest activity has been found in patients with hepatic metastases, despite the normality of other liver function tests.[10] One of the possible mechanisms responsible for BChE activity decrease in cancer patients could be secondary anorexia accompanying malignancy.[11]

The liver function test (LFT) enzymes play important metabolic roles in the functions of different cells and tissues of the gastrointestinal tract.[12] ALT, a cytosolic enzyme, and AST, both cytosolic and mitochondrial, is present in the sera of all age groups. These enzymes (transaminases) catalyze the reversible transfer of α-amine group of aspartic acid, alanine and α -keto group of ketoglutaric acid to form oxaloacetic acid, pyruvic acid and glutamic acid, respectively, via a specific electron transport system.[13,14] Such a biochemical mechanism helps maintain a normal and well-coordinated liver function.[12]

AST is present in both the cytoplasm and mitochondria of cells. In cases involving mild tissue injury, the predominant form of AST is from the cytoplasm, with a smaller amount coming from the mitochondria. During cancer progression, due to excessive reactive oxygen species (ROS) mitochondrial DNA damages.

This may cause severe tissue damage and results in more of the mitochondrial enzyme being released.[15] Significant elevation of AST/ALT ratio in advanced stages of the disease and also in larger tumor size could probably be associated with the degree of necrosis of the tumor.[16] The present study was attempted to find out the role of some of the biochemical markers like serum pseudocholinesterase (PCHE), serum aspartate transaminase (AST), and serum alanine transaminase (ALT), in malignancy of the uterine cervix.

## METHODS

This prospective study was conducted in Osmania General Hospital, Hyderabad by the Department of Biochemistry from August 2013 to September 2014. 60 patients aged between 30 -70 years who were having cervical cancer and admitted to our hospital were included into the study. 30 healthy patients within the same age group were included as controls. The nature of the study was explained in detail to all the patients and their relatives and informed consent was taken from all of them. Patients with organic phosphorus poisoning, any other malignancy, post-surgery, post-chemotherapy or post-radiotherapy patients of cervical cancer, recurrent cases of cervical cell carcinoma and patients with surgical illness and or serious medical conditions were excluded from the study.

5ml of venous blood was collected from all the study participants under aseptic conditions in a plain tube. Sample was centrifuged at 3000 rpm for 10min and serum was separated within two hours of collection of blood. Care was taken to prevent hemolysis of the samples. Lipaemic and icteric samples were discarded. Serum Pseudocholinesterase, Serum Aspartate transaminase and Serum Alanine transaminase was estimated for all the patients in both the groups.

Serum Pseudocholinesterase was estimated using New DGKC method. Cholinesterase catalyses the hydrolysis of butyrylthiocholine substrate forming butyrate and thiocholine. The working reagent and the sample were mixed and incubated at 370C for 30 seconds and the change in absorbance per 30 seconds during 90 seconds was measured. The decrease of absorbance is followed at 405nm and is proportional to the activity of cholinesterase in the sample.

Serum Aspartate transaminase was measured using Modified IFCC method. Aspartate aminotransferase (AST) catalyses the transfer of the amino group from L-aspartate to α - ketoglutarate to yield Oxaloacetate and L-glutamate.

The Oxaloacetate undergoes reduction with simultaneous oxidation of NADH to NAD in the malate dehydrogenase (MDH) catalyzed indicator reaction. The resulting rate of decrease in absorbance at 340nm directly proportional to the AST activity. Lactate dehydrogenase (LDH) is added to prevent interference from endogenous pyruvate which is normally present in serum. The reagent incorporates a reaction mechanism of regenerating the NADH for the extended stability of the working reagent.

Alanine transaminase is estimated using Modified IFCC method. Alanine aminotransferase (ALT) catalyses the transfer of the amino group from L-Alanine to α-ketoglutarate forming Pyruvate and L-glutamate. Pyruvate in the presence of NADH and Lactate dehydrogenase (LDH) is reduced to L-lactate. In this

reaction NADH is oxidized to NAD. The reaction is monitored by decrease in absorbance at 340nm due to the oxidation of NADH to NAD. The reagent incorporates a reaction mechanism of regenerating the NADH for the extended stability of the working reagent.

The data was analyzed by using Graph pad prism version 6 and Microsoft Excel software. The results were expressed as Mean and Standard deviation (SD). Independent sample 't' test was used to assess the significance of difference of means between the cases and controls, P<0.05 is considered as significant.

The results were represented in the form of Tables and Figures.

## RESULTS

The mean value of pseudocholinesterase in cervical cancer patients was lower in the cases when compared to controls and it was statistically significant (P value 0.0005), while the mean value of serum AST and ALT were higher in cases when compared to controls and it were also statistically significant (Table 1).

**Table 1: Mean, SD and significance of serum PChE, AST and ALT in cervical cancer patients and controls.**

| Parameter | Groups | Minimum | Maximum | Mean | Std. deviation | p value |
|---|---|---|---|---|---|---|
| PChE (U/L) | Cases (60) | 1104 | 9827 | 4660 | 2538 | 0.0005 |
| | Controls (30) | 5101 | 10762 | 6462 | 1324 | |
| SGOT(AST) (U/L) | Cases (60) | 21 | 86 | 50.60 | 16.61 | 0.0001 |
| | Controls (30) | 25 | 36 | 30.43 | 3.224 | |
| SGPT(ALT) (U/L) | Cases (60) | 20 | 77 | 50.28 | 15.25 | 0.0001 |
| | Controls (30) | 26 | 42 | 34.47 | 4.329 | |

When compared with Pearson's coefficient, the serum PChE had a significant negative correlation with AST and ALT, while the serum AST had a significant positive correlation with ALT and a negative correlation with Pche (Table 2).

**Table 2: Pearson's coefficient between PChE, AST and ALT.**

| | Number of cases | Pearson's correlation | p value |
|---|---|---|---|
| PChE - AST | 60 | -0.838 | 0.001 |
| PChE - ALT | 60 | -0.729 | 0.001 |
| AST – ALT | 60 | 0.882 | 0.001 |

## DISCUSSION

HPV is the most important aetiological factor, with most (99.7%) tumours containing HPV DNA.[17] Peak infection incidence is in the late teens and early 20s, but in 80% of patients, the infection resolves within 12 to 18 months with a median duration of infection of roughly 8 months.[18] The HPV virus is cleared by the immune system in 93% patients by 3 years post-infection. The incubation from latent infection to presentation with cancer is typically 15 years. The largest meta-analysis reported an annual rate of progression of high-grade squamous intraepithelial lesion to invasive cancer of 1.4%.[19]

Pap smear in invasive cancer shows tadpole cells, fibres and malignant cells and haemorrhage, and necrosis in the background. It is customary to identify two types of cancers of the cervix. The first and more common variety is the epidermoid carcinoma. It arises from the stratified squamous epithelium of the cervix, and accounts for almost 80% of all cancers in the cervix. The second variety, endocervical carcinoma, arises from the mucous membrane of the endocervical canal, and accounts for 20% of all cervical cancers. Histologically, 95% of cervical cancers are squamous carcinomas and only 5% are adenocarcinomas. This is because the columnar epithelium of the endocervix often undergoes squamous metaplasia.[20]

Early detection of cervical cancer improves quality of life for affected patients. Identification of molecular markers (or biomarkers) which can predict disease progression is necessary for better management of this disorder.

In this study, we sought to estimate and compare serum BChE levels in healthy controls and patients with biopsy-proven cervical cancer before definitive therapy as radiotherapy or chemotherapy may alter the levels of BChE and may act as a confounding variable.

In the present study, Mean ± SD of Butyrylcholinesterase in controls was 5080.90 ± 817.7019(U/L), in cases was 2718.40±592.731(U/L) ($p < 0.001$). The pseudocholinesterase levels in patients decreased significantly (p value 0.001) when compared to controls. Decrease in pseudocholinesterse levels might be due to cancer induced inflammatory suppression of cytochrome P450 with decreased expression of mRNA and cytochrome protein synthesis.

In study by Bradamante et al 60 patients with recurrent cervical cancer had statistically significant lower values

of pseudocholinesterase (PChE) than 38 patients with benign tumours of the uterus ($p < 0.001$) and 30 patients with uterine cervical carcinoma. Their results have shown a similar direct relationship between the PChE activity and the degree of malignant disease.[21]

In another study by Arun Chougule, et al, it was estimated that serum pseudocholinesterase (PCHE) in 92 patients with head and neck cancer and 71 patients with cancer of the uterine cervix were lower than that in normal subjects. In a study b by orpollo low PChE activity was also found in 118 of 2215 surgical patients and out of 118 patients, 23 (19.5%) had malignancies (non-metastatic or metastatic).[22] In Santarpia et al study, BChE levels decreased in 152 advanced cancer patients with or without liver involvement and it were found that besides albumin levels and Karnofsky index, serum BChE levels were a survival predictive factor in terminal cancer patients with peritoneal carcinomatosis.[23]

In the present study, Mean ± SD of Aspartate transaminase in controls was 30.43 ± 3.224 (IU/L), in cases was 50.60 ± 16.61(IU/L), ($p < 0.001$) and the Mean ± SD of Alanine transaminase in controls was 34.47 ± 4.329 (IU/L) in cases was 50.28 ± 15.25 (IU/L) ($p < 0.001$) showing that the liver enzymes in cervical cancer patients increased significantly (p value 0.001) when compared to controls. Alteration in serum AST and ALT was due to degeneration and necrosis of liver cells which was accompanied by damage of cell walls and cytolysis and mitochondrial damage and release of enzymes.

A similar picture was observed in a study by Singh et al 193 gallbladder cancer patients had increased levels of both SGPT and SGOT.[12] This indicates an increase in the tissue-specific cellular physiology, most likely due to malignancy or long-term tissue inflammation. The transformed cells (after development of tumor) become malfunctional for most of the cellular pathways. As a consequence of advancement in the process of tumorigenesis, the functional levels of enzymes released become elevated in gallbladder cancer cells. SGOT and SGPT showed significantly elevated values in 80.49%, 77.68% in gall bladder cancer and gall bladder with stones respectively.[13] The finding of even modest increases of aminotransferase concentrations should not be overlooked as it could provide an opportunity for clinicians to reveal and treat not only serious hepatic diseases but also non-hepatic diseases.[24] Similar increase in these enzyme levels were seen in similar studies on various cancer patients, such as breast cancer, gall bladder cancer prostate and lung cancer.[25-28]

AST would be a significant and valuable prognostic factor for the survival duration of advanced cancer patients. Hui-Ju Tsai study revealed that two times higher AST and ALT levels, prolonged PT, and hypoalbuminemia are likely to be prognostic factors of poor survival in advanced cancer patients.[29]

PChE has significant negative correlation with AST and ALT. AST has significant positive correlation with ALT and has negative correlation with Pche. ALT has significant positive correlation with AST and has negative correlation with Pche. Since, in majority of thecervical cancer patients before treatment the Pche enzyme activity was low. The PChE concentration in plasma is therefore a reflection of the rate of its formation in hepatocytes, and any alteration of its activity can be an indication of cellular impairment.

## CONCLUSION

Among the women with cervical cancer, it was observed that the enzyme activity of PChE was lower than normal, while that of SGPT and SGOT were higher. Hence it can be inferred that low pseudo cholinesterase activity can be taken as good diagnostic marker for cervical cancer. PCHE, AST, and ALT can be used as tumor markers in the management of malignancy of the uterine cervix. These results also have clinical significance for the anaesthesiologist. These facts about the influence of advanced stages of the malignant disease on PChE activity are important for the anaesthesiologist in case a planned or emergency surgery in these patients is required.

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