CASEIN KINASE 2 AND SURVIVIN MODULATION IN PROSTATE AND BREAST CANCER

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ABSTRACT

Objective: To find out whether Casein Kinase 2 (CK2) and Survivin co-express and correlate in prostate as well as in breast cancer.

Study Design: A cross sectional analytical study.

Place and Duration of Study: Study was done at Army Medical College and in collaboration with Armed Forces Institute of Pathology (AFIP). The duration of this research was two years.

Material and Methods: The research was authorized by the Ethical Committee of AFIP. CK2 expression was determined by immunohistochemistry in paraffin embedded tissues from established patients of prostate cancer (n=30) and breast adenocarcinoma (n=30). Correlation of CK2 with Survivin was evaluated. Data were analyzed through SPSS version 20. For studying the correlation between the two proteins, pearson correlation coefficient was calculated. Data was considered at *p*-value ≤0.05.

Results: An expressively strong and affirmative correlation was found among expression of total CK2 and total Survivin in invasive along with non-invasive cases of both prostate and breast cancers. A significantly strong and positive correlation was found between nuclear CK2 and Survivin expression in non-invasive cases of prostate cancer and invasive as well as non-invasive cases of breast cancer. A significantly strong and positive correlation was found only between cytoplasmic CK2 and Survivin expression in non-invasive cases of prostate cancer.

Conclusion: CK2 and Survivin expressions have strong and positive correlation in both prostate and breast cancer particularly in non-invasive stage of the cancer.

Keywords: Breast cancer, CK2, Co-expression, Prostate cancer, Survivin.

INTRODUCTION

Cancer is the distinguished reason of death globally killing about 7.4 million population in 2004[1]. Common diseases among elderly males include prostate cancer & benign prostatic hyperplasia (BPH)[2]. For prostate cancer, the prognostic biomarker availability is limited i.e. currently serum Prostate Specific Antigen (PSA)[3]. The focus of study was to find out prognostic markers in prostate cancer. Little attention has been paid in the past to determine the mechanisms at molecular level that are responsible for cancer initiation as well as progression[4]. Moreover breast cancer is very common in females belonging to both developed and under developed countries. It has killed more than 508,000 females in year 2011[5]. Researchers have been focusing to find the tumor markers for breast cancer, that are important for prognosis, treatment options, rate of survival and association with its sub-types[6] e.g. HER2[7].

Cancer development is the result of changes that occur in microenvironment of the cell. The changes include inflammation, oxidative stress and damage to DNA[8]. Recent cancer biology states that in normal mammalian cells, common signaling pathways are simultaneously controlling cell reproduction, survival and cell death. Disturbance of signaling network can lead to cancer[9].

CK2 role in neoplasias is a hot issue of research[10]. Elevation in expression of CK2 is found in cancers[11]. CK2, a serine/threonine kinase[12] along with apoptotic inhibitory proteins, has a role in promoting cancer[13]. Elevated

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expression of CK2 in cancers and its ability to support tumorigenesis makes it a candidate target for cancer therapy[14].

Survivin, an inhibitor of apoptosis has elevated expression in cancers and is associated with poor outcome from clinical point of view[15]. High expression of CK2 α is found to up-regulate the Survivin expression via β-catenin-Tcf/Lef and these effects were found to be abolished by TBB. Similarly CK2α down-regulation resulted in reduced β-catenin as well as Survivin level concluding that survival was enhanced by increased CK2 and Survivin levels[16].

Table: Comparison of IHC data of CK2 and Survivin in prostate and breast cancer tissues (already published data[17,18]).

Proteins expression and localization	Groups	Prostate Cancer			Breast Cancer		
		N	Mean ± S.D	*p*-value	N	Mean ± S.D	*p*-value
CK2 Nucleus	Non-Invasive	11	1.64 ± 0.80	0.267	10	1.40 ± 0.52	0.100
	Invasive	19	1.26 ± 0.93		20	1.90 ± 0.85	
CK2 Cytoplasm	Non-Invasive	11	1.54 ± 0.522	0.682	10	0.80 ± 0.63	0.619
	Invasive	19	1.63 ± 0.60		20	0.95 ± 0.83	
CK2 Total	Non-Invasive	11	5.45 ± 1.92	0.605	10	2.20 ± 1.03	0.202
	Invasive	19	5.05 ± 2.07		20	2.85 ± 1.39	
Survivin Nucleus	Non-Invasive	11	3.47 ± 0.45	<0.001	10	2.6 ± 3.5	0.491
	Invasive	19	2.82 ± 0.31		20	3.6 ± 3.8	
Survivin Cytoplasm	Non-Invasive	11	1.63 ± 0.92	0.21	10	4.6 ± 2.5	0.009
	Invasive	19	1.27 ± 0.63		20	1.5 ± 3.03	
Survivin Total	Non-Invasive	11	1.11 ± 0.76	0.92	10	6.6 ± 3.6	0.462
	Invasive	19	1.09 ± 0.26		20	7.7 ± 3.9	

Based on the literature and in order to solve the mysteries related to pathways initiating or promoting cancer, the study was designed and aimed to evaluate the co-expression and correlation of CK2 with Survivin in prostate and breast cancers (Published data[17,18]). The present article is focused to compare the co-expression and correlation of CK2 and Survivin in both prostate as well breast cancers.

MATERIAL AND METHODS

It was a cross sectional analytical study. The duration of research was two years and it was carried out at Army Medical College (AMC) Rawalpindi. Paraffin embedded tissues of 30 diagnosed cases of prostate cancer and breast cancer each, were chosen, by non-probability convenience sampling. Study was authorized by the Ethical Committee of Armed Forces Institute of Pathology (AFIP). Samples were obtained from Armed Forces Institute of Pathology. CK2 expression was obtained by immuno-histochemistry.

Data were analyzed in SPSS version 20. Descriptive statistics was calculated. Mean and standard deviation were calculated for quantitative variables. Categorical variables were presented by percentage. Correlation between CK2 and Survivin was determined. Pearson's correlation coefficient was calculated. Independent t-test was applied for the comparison between groups for normal variables. For non-normal variables non parametric test was applied. A *p*-value less than 0.05 considered as a significant value.

RESULTS

Among the 30 prostate cancer tissues, 30% patients had lympho-vascular invasion whereas 50% patients had perineural invasion. Mean Gleason score was found to be 7.33 (SD ± 1.124). Among the 30 breast cancer tissues, 20 patients had perineural invasion. Mean Nottingham index score in breast cancer patients was 6.0 (SD ± 1.17) among invasive cases whereas 4.06 (SD ± 0.751) among noninvasive cases (data already published[17,18]).

CK2 and Survivin data as published before[17,18] is presented in table. A significantly strong and positive correlation was found between expression of total CK2 and total Survivin in invasive as well as non-invasive cases of both prostate and breast cancer (fig-1). A significantly strong and positive correlation was found between nuclear CK2 and Survivin expression in non-invasive cases of prostate cancer and invasive as well as non-invasive cases of breast cancer (fig-2). A significantly strong and positive correlation was found only between cytoplasmic CK2 and Survivin expression in non-invasive cases of prostate cancer (fig-3).

DISCUSSION

CK2 overexpression is evident in cell, in all of the proliferative states. Deregulated expression of CK2 in association with some oncogenes, enhances tumor phenotype[19]. It plays important role in various cellular processes and has above 300 substrates[20]. Its expression is higher in human cancers[21], but the mechanism of its participation in carcinogenesis is still unclear[22].

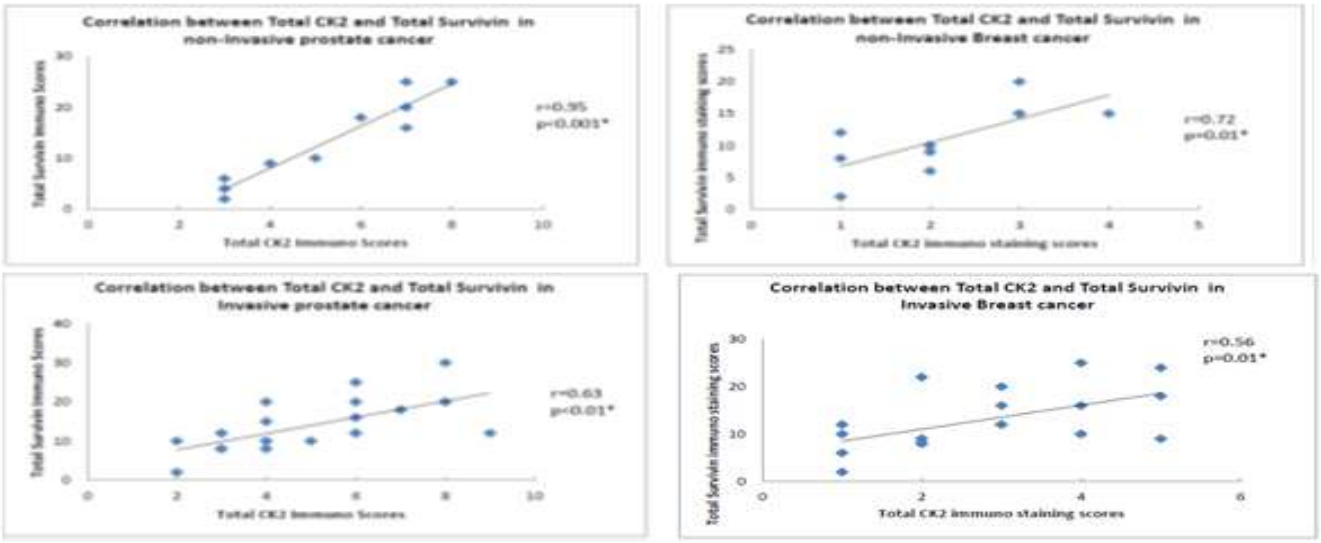

Figure-1: Correlation of total CK2 and survivin expression in prostate and breast cancer tissues.

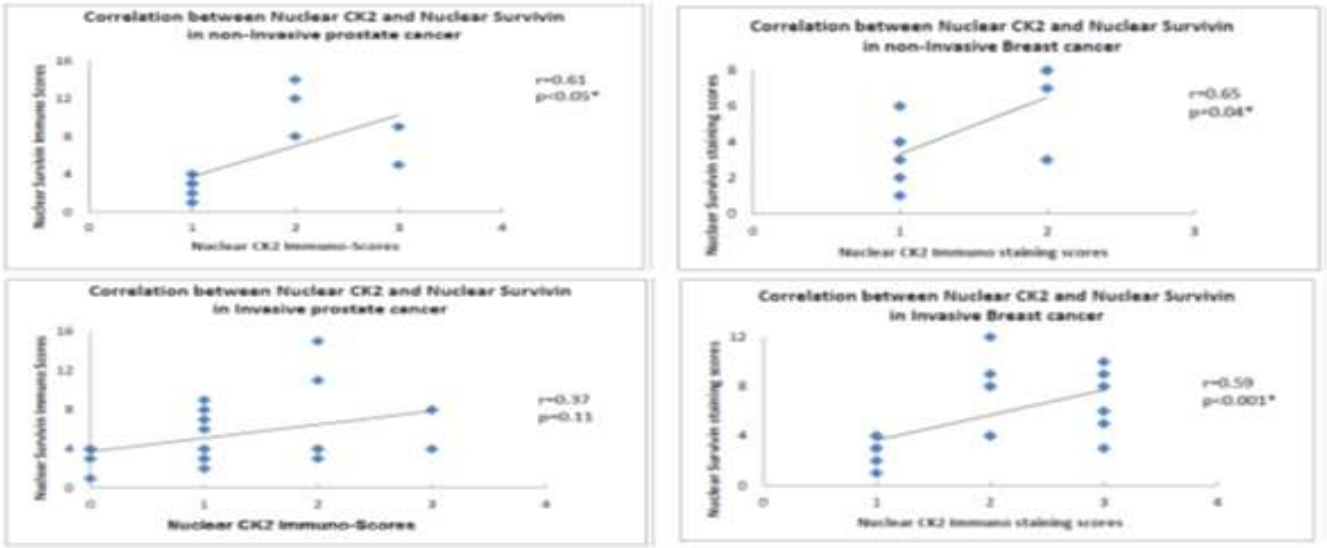

Figure-2: Correlation of nuclear CK2 and survivin expression in prostate and breast cancer tissues.

CK2, a master player in the development of cancer, is a sword with double edge. It not only enhances proliferation but also inhibits apoptosis[10]. Survivin has implications in tumorigenesis as its activity is related to inhibition of apoptosis, progression of cell cycle, metastasis and higher angiogenesis. It is observed that CK2 promotes tumor cell viability by increasing the Survivin expression. Besides this, overexpression of Survivin alone was sufficient to revert effects of CK2 inhibition on viability of cell[23]. Hence in tumors, Survivin is identified as a crucial downstream target by CK2[24].

For this purpose, we evaluated the involvement of CK2 with Survivin in pathogenesis of both prostate and breast cancers (already published data[17,18]). Presently we are comparing the findings of Survivin and CK2 expression and correlation in both cancers to analyze the pattern they follow. We observed that total CK2 and Survivin expression levels are significantly and strongly correlated in invasive and non-invasive cases of both prostate as well as breast cancers. The nuclear expression of both proteins is strongly correlated in non-invasive phenotype of both cancers, indicating that this association is more prominent in early cancer. Our observations are in line with the previous findings. Over expression of CK2α has been correlated with expression of Survivin previously[25]. CK2 plays a role in modulation of the apoptotic activity through the IAPs (apoptosis inhibitory proteins)[26] and it is evident that CK2 mediates the up-regulation of Survivin leading to enhanced survival of the cell and tumorigenesis[27]. It has also been observed through CK2 inhibition study that in prostate cancer cells, inhibiting CK2 lead to decreased expression of Survivin[28].

This data suggests that CK2 and Survivin are associated with one another to promote tumorigenesis especially in early cancer stage of both the prostate and breast cancers. This may form the basis and provide a platform for invasion and metastasis of the cells with deregulated expression. This study has improved the understanding of CK2 function and deregulation and supports the current research focused to characterize CK2 as a strong therapeutic target in cancer treatment.

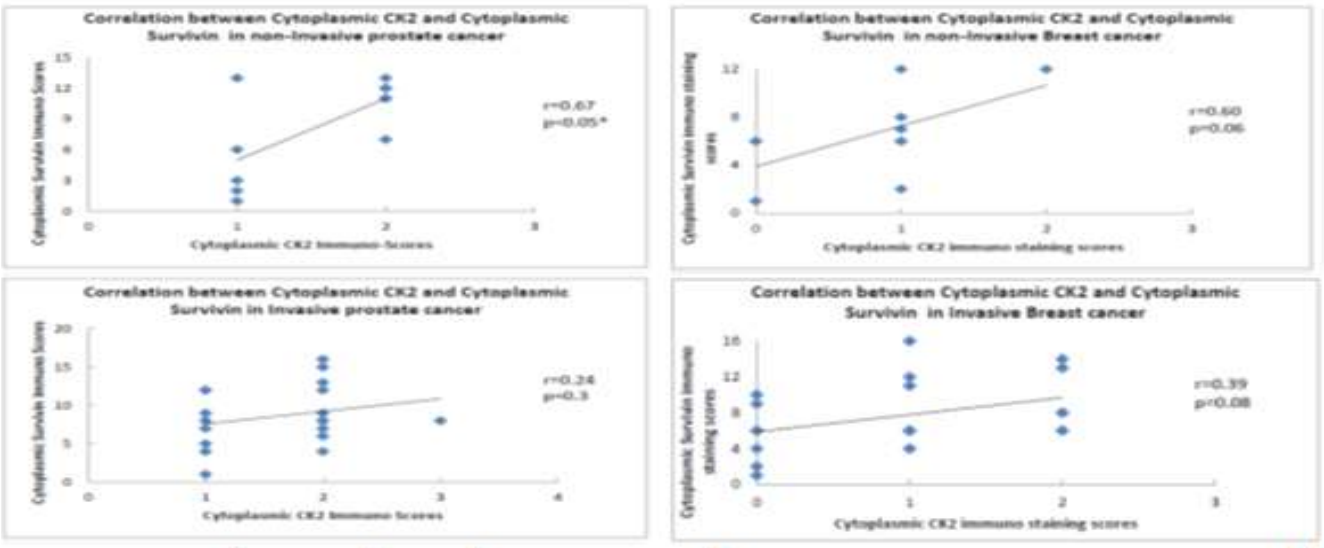

Figure-3: Correlation of cytoplasmic CK2 and survivin expression in prostate and breast cancer tissues.

CONCLUSION

CK2 and survivin expression have strong and positive correlation in both the prostate and breast cancer particulalry in non-invasive stage of the cancer.

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CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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