Original Article

Squamous Cell Carcinoma Antigen Reproducible Marker and Its Clinicopathological Correlation with Preinvasive and Invasive Cervical Cancer

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Abstract

Background: Squamous cell carcinoma antigen (SCC-Ag) is a serologic tumor marker detected in SCC of the cervix. The aim of this study is clinical features and their histopathological correlation between preinvasive and invasive cervical cancer and its association with SCC-Ag levels. **Materials and Methods:** This case–control study was carried out over a period of 1 year in the Department of Obstetrics and Gynaecology, with collaboration of pathology and medicine. After informed consent and ethical clearance, totally 3200 women were recruited. Out of these, 76 women who were histopathological proven, 30 preinvasive, and 46 of invasive cervical malignancy (International Federation of Gynecology and Obstetrics Stage I–IV) enrolled for study. 15 healthy cytology negative were considered as controls. Per speculum, per vaginam examination was done in every women and pap smear was obtained. Pretreatment 5 ml venous blood samples were drawn into sterile vials. SCC-Ag levels were measured by enzyme-linked immunosorbent assay (ELISA) technique using ELISA Kit as per producer protocol. **Results:** Among preinvasive group, 35.46% women complained white discharge per vaginam. Blood mixed discharge and postcoital bleeding were observed in 3.4% and 0.71%, respectively. In malignant group, foul smelling discharge and postmenopausal bleeding were reported in 1.68% and 1.87% women, respectively. Serum SCC-Ag levels were increased from controls to cases. In controls, 0.27 ± 0.12 ng/ml, preinvasive 0.85 ± 0.37 ng/ml and in invasive malignancy Stage I, II, III, IV, 2.10 ± 0.55 ng/ml, 3.15 ± 0.84 ng/ml, 4.12 ± 0.89 ng/ml, and 2.71 ± 1.05 ng/ml, respectively. Moderately differentiated and poorly differentiated SCC were reported in 80.43% and 19.56%, respectively. Expired patients had significantly ($P < 0.01$) higher premean SCC Ag level as compared to those who remain alive. **Conclusion:** Serum SCC-Ag is not only useful in the detection of preinvasive lesions and early invasive cases of cervical cancer but also a definite indicator for advanced Stage malignancy. Its value was quite high in late stages of cervical malignancy, thus it can be used as reproducible marker in cervical cancer.

Keywords: *Cervical cancer, cervical intraepithelial lesion, clinicopathological correlation, squamous cell carcinoma antigen*

Introduction

Cancer is one of the leading causes of death worldwide. Every year, approximately 14 million new cases are detected, and 8 million people die because of cancer.[1] Cervical cancer is a major public health problem in developing countries like India.

India has a population of 432.2 million women aged 15 years and older who are at the risk of developing cervical cancer. It is the second most common cancer in women aged 15–44 years. Every year in India, 122,844 women are diagnosed with cervical cancer and 67,477 die from the disease.[2] It is estimated that cervical cancer will occur in approximately 1 in 53 Indian women during their lifetime compared with 1 in 100 women in developed country.[3]

Squamous cell carcinoma antigen (SCC-Ag) is a glycoprotein. It is a subfraction of TA-4, a tumor-associated antigen first described by Kato *et al*. in 1987.[4] It belongs to the family of serine protease inhibitors. It has two isoform, neutral isoform is detected in both normal epithelial cells and malignant tissues whereas the acidic isoform is found in periphery of the tumor, and in the sera of cancer patients with well-differentiated SCC.[5,6] India is a developing country and here human papillomavirus (HPV) screening routinely not practiced. HPV belongs to papillomaviridae family of nonenveloped DNA viruses.[7] HPV is

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the most common sexually transmitted virus in both men and women.[8] This virus usually affects mucosa and cutaneous keratinocytes. On the basis of oncogenic potential, they are classified into low-risk HPV types causing condyloma and warts, and high-risk HPV infect anogenital region and responsible for malignant lesions and cervical malignancy.[9,10] High-risk HPV strains such as 16 and 18 causes about 70% of cervical cancers[11,12] No definite prognostic marker for cancer cervix are available. Thus, still, the challenge in the present scenario is to have low-cost tumor marker, which could predict the probability of progression from preinvasive to invasive stage.

For this purpose, this present study was planned to evaluate the clinical features and their histopathological correlation in preinvasive and invasive cervical cancers and its association with SCC-Ag levels.

Materials and Methods

This prospective case–control study was carried out over a period of 1 year in the Department of Obstetrics and Gynaecology, in collaboration with the Department of Pathology and Department of Medicine at King George Medical University, Lucknow, Uttar Pradesh India. After informed consent and ethical clearance total, 3200 women were recruited. Out of these, 76 women who were histopathological proven, 30 preinvasive, and 46 invasive cervical malignancy (International Federation of Gynecology and Obstetrics [FIGO] Stage I–IV) enrolled for the study. Fifteen healthy cytology-negative women were taken as controls.

Histopathologically, proven preinvasive and invasive cervical cancer patients were included in this study. Women who were not willing to participate or with SCC of vulva, vagina, head and neck, esophagus, SCC of lung, sarcoidosis, tuberculosis, benign disease of skin-like psoriasis, pemphigus, and women suffering from renal failure were excluded from the study.

Every women who came in outdoor with discharge per vaginam, postcoital bleeding, and postmenopausal bleeding underwent per speculum and per vaginam examination. Per rectal examination was done in women with suspicion of malignancy or if frank malignant growth was present. During per speculum examination, Pap smear taken by Ayer's spatula rotating 360° over external os of the cervix at squamocolumnar junction. Women with unhealthy cervix subjected for colposcopy and every suspicious lesion underwent a biopsy to rule out cervical intraepithelial neoplasia. Cervix with obvious growth punch biopsy had been taken directly from junction of healthy and unhealthy areas. Tissues were sent for histopathological examination, and histological types of tumors and grade of tumors were recorded.

Clinical FIGO staging was done in women with invasive cervical cancer, parametrial involvement was determined by pelvic and per rectal examination at the time of diagnosis. Complete blood count, blood urea, serum creatinine, liver function test, chest X-ray, cystoscopy, and computed tomography were done. SCC-Ag levels were measured using ELISA Kit. Ethical clearance was obtained from the Institutional Ethics Committee. Details of the patients were recorded in predetermined questionnaire pro forma that included sociodemographic details, history of present illness, menstrual history, systemic examination finding and per speculum, pervaginam, and per rectal examination findings in suspected malignancy.

Squamous cell carcinoma antigen estimation by enzyme-linked immunosorbent assay method

Five milliliter venous blood samples were drawn into a sterile vial from all patients before treatment. Samples were kept at 4°C, centrifuged at 6000 rpm for 15 min, and then immediately frozen at −20°C until assay. Serum SCCAg levels (SCC-Ag2) were estimated by sandwich ELISA technique using ELISA kit for *in vitro* quantitative measurement as per producer protocol (USCN life sciences Inc., Export Processing zone, Economic and Technological development zone, China).

The microtiter plate of kit has been precoated with an antibody specific to SCC-Ag2. Standard and sample are then added to the appropriate microtiter plate wells coated with a biotin-conjugated antibody preparation specific for SCC-Ag2. Avidin conjugated to HRP is added to each microplate well and incubated. After 3, 5, 3'5tetramethylbenzidine substrate solution is added, only those wells that contain SCC-Ag2, biotin-conjugated antibody, and enzyme-conjugated avidin exhibited a change in color. The enzyme-substrate reaction is terminated by the addition of sulfuric acid solution, and the color change is measured spectrophotometrically at a wave length of 450 nm ± 10 nm. The concentration of SCC-Ag2 in the sample is then determined by comparing the optical density of the sample to the standard curve.

Statistical analysis

Data obtained had been subjected to statistical analysis. The data were summarized as mean ± SD Groups were compared by one-way analysis of variance (ANOVA) and the significance of mean difference between the groups was done by Tukey's *post hoc* test. Groups were also compared by factorial two-way ANOVA, and the significance of mean difference within and between the groups was done by Tukey's *post hoc* test. Groups were also compared by repeated measures ANOVA. Discrete (categorical) groups were compared by Chi-square test. A two-sided ($\alpha = 2$) ($P < 0.05$) was considered statistically significant. All analyses were performed on STATISTICA software (Windows version 6.0) Dell Software.

Results

Total 3200 women recruited for the study, preinvasive lesions were detected in 30 women, invasive lesions were

found in 46 women. 15 women were taken as control [Table 1].

In present study, 35.46% had white discharge per vaginam, 3.4% had blood mixed discharge, 0.71% women had postcoital bleeding which was common symptom among preinvasive group. In malignant group, 1.68% had foul smelling discharge, 1.87% postmenopausal bleeding, and constitutional symptom were common in advanced malignancy. 14 patient had endometrial malignancy. The rest 33.43% women presented as pain in the abdomen and 20.93% were asymptomatic [Table 1].

Most women had healthy cervix during per speculum examination. 18.84% women had cervical erosion, 9.96% women had ectropion, polyp was found in 3.28% women, and 6.62% women had hypertrophied cervix. 1.9% % women had frank cervical growth [Table 2].

In our study, rising trend of mean SCC-Ag levels was observed from controls to preinvasive stage to invasive stages. The premean SCC-Ag level of CIN III group significantly ($P < 0.01$) different and higher as compared to controls. However, the pre mean SCC-Ag in all preinvasive stages was <2 ng/ml [Table 3].

Among invasive malignancy group, mean SCC-Ag level of Stage I to Stage IV cases were significantly higher ($P < 0.001$) as compared to both controls and CIN. The mean SCC-Ag levels of Stage III cases were significantly ($P < 0.001$) higher as compared to Stage I, Stage II, and Stage IV cases [Table 3].

Increase in SCC-Ag level was observed as the disease advances. SCC-Ag level was higher in those women whose parametrium was involved as compared to those whoes parametrium not involved on per vaginam and per rectal examination. SCC-Ag level 3.78 ± 0.077 ng/ml was found with lymph node involvement group as compared to negative lymph node group i.e., 2.41 ± 0.78 ng/ml. Even the SCCAg level was more higher where hydronephrosis and bladder involvement was present (>4 ng/ml) [Table 4].

Out of 46 cancerous women, 37 (80.43%) were of moderately differentiated, and 9 (19.56%) cases were of poorly differentiated cervical cancer, mean SCCAg level was higher in poorly differentiated carcinoma as compared to moderately differentiated carcinoma, but this difference was statistically not significant [Table 5].

Mean SCC-Ag level was high 4.67 ± 1.43 ng/ml among those patients who expired as compared to live patients 2.78 ± 1.14 ng/ml, this difference was statistically significant ($P < 0.01$) [Figure 1].

Table 1: Symptoms of all (3200) recruited women (*n*=3200)

Symptoms	*n* (%)
Asymptomatic	670 (20.93)
Pain in abdomen	1070 (33.43)
White discharge per vaginam	1135 (35.46)
Blood mixed discharge	110 (3.4)
Foul smelling discharge	54 (1.68)
Postcoital bleeding	23 (0.71)
Postmenopausal bleeding	60 (1.87)
Constitutional symptom	78 (2.43)

Table 2: Finding of 3200 recruited women on examination (*n*=3200)

Findings	Cases, *n* (%)
Healthy cervix (1900)	1900 (59.3)
Unhealthy cervix (1300)	
Cervical erosion	603 (18.84)
Ectropion	319 (9.96)
Cervical polyp	105 (3.28)
Hypertrophied cervix	212 (6.62)
Frank growth	61 (1.9)
Normal pap smear	2249 (70.28)
Abnormal pap smear	890 (27.81)
Normal colposcopy	609 (19.03)
Abnormal colposcopy	281 (8.78)

Table 3: Distribution of subjects between control, preinvasive and invasive cervical cancer and their mean squamous cell carcinoma antigen levels

Signs	Cases (*n*=91), *n* (%)	Pre-SCC-Ag level (mean±SD)
Healthy cervix	15 (16.48)	0.27±0.12
Unhealthy cervix		
Preinvasive lesion - 30		
CIN I	8 (8.79)	0.43±0.05
CIN II	10 (10.98)	0.75±0.14
CIN III	12 (13.18)	1.22±0.24
Invasive lesion - 46		
Stage I	8 (8.79)	2.10±0.55
Stage II	15 (16.48)	3.15±0.84
Stage III	15 (16.48)	4.12±0.89
Stage IV	8 (8.79)	2.71±1.05

SD: Standard deviation, SCC-Ag: Squamous cell carcinoma antigen, CIN: Cervical intraepithelial neoplasia

Discussion

Cervical cancer is the most common cause of cancer-related death in developing countries.[13] Cervical cancer is a preventable disease because before cancerous stage, long silent period of preinvasive stage always present. Despite the development of so many screening methods, none of them could predict the progressive nature of the cervical neoplasia. Still, major challenges exist to find out the low cost and simple prognostic marker of cancer cervix which could help in early identification of the progressive lesions and its appropriate management. Tumor marker which facilitates early diagnosis also offers a guide for the evaluation of prognosis, and in another

Table 4: Squamous cell carcinoma antigen level measurement in cervical cancer (International Federation of Gynecology and Obstetrics - I-IV) with clinical variable

Condition	Mean±SD			Significance of difference	
	Before treatment	After treatment	Percentage change	*t*	*P*
Overall (*n*=46)	3.31±1.10	1.12±0.62	66.50±12.18	16.803	<0.001
Per speculum findings					
Microinvasive erosion (*n*=8)	2.10±0.55	0.50±0.08	61.65±12.12	8.233	<0.001
Tumor size <4 cm (*n*=13)	3.58±1.24	1.38±0.72	66.57±11.20	9.070	<0.001
Tumor size >4 cm (*n*=25)	3.67±0.76	1.21±0.50	73.25±11.54*	13.851	<0.001
Stage					
Stage I/II (*n*=23)	2.78±0.89	0.97±0.62	66.03±12.87	14.833	<0.001
Stage III/IV (*n*=23)	4.12±0.89	1.35±0.57	67.23±11.44	14.167	<0.001
P/V parametrium involvement					
No (*n*=15)	2.82±0.86	0.90±0.69	69.87±12.45	14.663	<0.001
Yes (*n*=31)	3.63±1.13	1.26±0.55	64.30±11.75	12.466	<0.001
P/R status					
Negative (*n*=15)	3.22±1.14	1.11±0.65	66.14±12.37	15.06	<0.001
Positive (*n*=31)	3.81±0.77	1.18±0.50	68.42±11.98	8.270	<0.001
Lymph node involvement (CT)					
Negative (*n*=13)	2.41±0.78	0.67±0.24	70.95±10.82	9.281	<0.001
Positive (*n*=33)	3.78±0.95	1.35±0.64	64.19±12.40	15.682	<0.001
Hydronephrosis (USG)					
No (*n*=25)	2.74±0.91	0.96±0.65	66.33±12.39	14.871	<0.001
Yes (*n*=21)	4.01±0.91	1.31±0.55	66.71±12.29	14.025	<0.001
Bladder involvement (cystoscopy)					
No (*n*=37)	3.56±0.97	1.30±0.62	63.40±11.39	16.370	<0.001
Yes (*n*=1)	4.40	0.98	77.73	-	-

CT: Computed tomography, USG: Ultrasonography, SD: Standard deviation, P/V: Pervaginal examination, P/R: Perrectal examination

Table 5: Distribution of subject according to histopathological finding and association with squamous cell carcinoma antigen level

FIGO stage	Moderately differentiated (*n*=37)	Pre-SCC-Ag, ng/ml (mean±SD)	Poorly differentiated (*n*=9)	Pre-SCC-Ag, ng/ml (mean±SD)	*P*
Stage I	8	2.88±1.35	0	3.36±0.87	0.316
Stage II	11		4		
Stage III	11		4		
Stage IV	7		1		

FIGO: International Federation of Gynecology and Obstetrics, SD: Standard deviation, SCC-Ag: Squamous cell carcinoma antigen

word, this would help in selection of patients for adjuvant chemotherapy.

Mostly, women with early cervical malignancy were asymptomatic; some presented with vaginal bleeding, postcoital bleeding or rarely vaginal mass, blood mixed vaginal discharge. Symptoms of advanced cervical cancer may include loss of appetite, weight loss, fatigue, pelvic pain, back pain, leg pain, heavy bleeding from the vagina, rarely leakage of urine, or feces from the vagina.[14]

One study reported white discharge was the first and most common complaint in more than 50% of patients with malignancy.[15] In the present study, most common symptom was white discharge per vaginam found in 35.46% women and postmenopausal bleeding was found in 1.87% women.

Various authors reported most common complaint was bleeding irregularities followed by discharge per vaginam.[16-18] In the present study, 0.71% patients had postcoital bleeding, 3.4% complaint blood mixed discharge, and 1.68% had foul smelling discharge. Maximum symptoms were observed in women with invasive cervical cancer.

Constitutional symptoms such as loss of weight, loss of appetite, and backache were observed in 2.43% where as other study reported backache and pain abdomen in 5.68% and 31.03% cases, respectively.[19]

Out of studied women, most women reached to hospital with frank malignancy (50.54%), in which 16.48% presented in Stage IIB and IIIB and 8.79% in stage IV. This is might be because of illiteracy and lack of awareness and had very less knowledge about the health and hygiene.

In our study, mean SCC-Ag levels were increased as the clinical stage of cervical cancer advances, but less change was observed with preinvasive lesions with level below

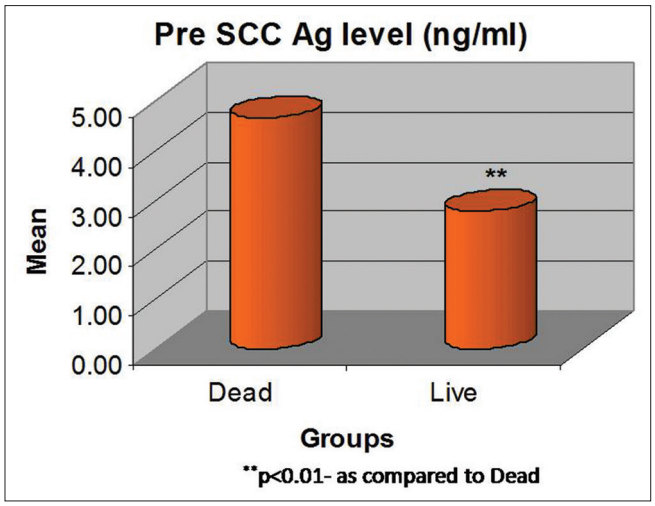

Figure 1: Outcome wise summary of premean squamous cell carcinoma antigen level among patients of (International Federation of Gynecology and Obstetrics stage I–IV)

2 ng/ml. One study reported only14.3% patients with CIN III had SCC-Ag level above 2 ng/ml.[20]

Here, premean SCC-Ag level of Stage I to IV cases was significantly higher ($P < 0.001$) as compared to both control and CIN. One author reported pretreatment SCC-Ag was higher in the higher stage of SCC.[21] One study reported elevated SCC-Ag in Stage I SCC 37.1% patients, stage II 70.0% patients, and in stage III 90% patients and the significantly higher SCC-Ag level was found in Stage III cervical cancer ($P < 0.1$).[22]

In our study, SCC-Ag level of Stage IV was less than Stage III. SCC-Ag is produced by the peripheral regions of the tumor and not by all the cancer cells in a tumor. This might elevated serum SCC-Ag concentration is not related with T factor in SCC.[23] SCC-Ag was higher in Stage 4B (SCC-Ag-5.2 ng/ml) in comparison to Stage IVA. However, limitation of our study is that only one case of Stage IVB was present.

SCC-Ag level was higher in those women whose parametrium was involved as compared to without involvement on per vaginam and perrectal examination. Higher SCC-Ag level was observed in women with lymph node involvement than negative lymph node. The SCCAg level was more higher where hydronephrosis and bladder involvement present (>4 ng/ml). Other studies also reported SCC-Ag significantly correlate with tumor stage, deep stromal invasion, and lymph node involvement in cervical cancer.[24,25]

On the other hand, few author reported SCC-Ag and CA 125 are not suitable for early detection of disease. They did not find a correlation between tumor marker levels and tumor size, for SCC and adenocarcinoma.[26]

In our study, SCC-Ag level in poorly differentiated cancer was quite higher as compared moderately differentiated cancer. Contrary, other author reported that close relation of SCC-Ag with squamous epithelium tumor and its raised level was more associated with more differentiated type of carcinoma.[23]

As per other study, there was no significant difference in the incidence of positive serum SCC-Ag concentration between undifferentiated type and more differentiated type of carcinoma.[24]

This present study showed higher SCC-Ag level in women who were expired during follow-up as compared to alive patients, and this difference was statistically significant ($P < 0.01$).

One author found that a pretreatment SCC-Ag level greater than 10 μg/L had a significant impact on survival in Stage I to IVA squamous cell cervical cancer primarily treated with radiotherapy.[27]

One study has shown that a high pretreatment serum SCC level (>8 μg/L) dramatically increases the likelihood of lymph node metastases or extracervical spread (metastases or extracervical spread).[28]

Another author had reported pretreatment SCC-Ag level was the only independent risk factor for poor survival in 260 patients with Stage IB or IIA disease.[25]

The result of this study suggested that a combination of clinical feature and SCC-Ag levels might be good for diagnostic purpose and it provides useful information for the assessment of cervical cancer progression.

Conclusion

Serum SCC-Ag antigen is most valuable marker for cervical cancer, especially in advanced stage, higher pre-SCC-Ag value helpful in diagnosing progression. Screening of cervical cancer should be emphasized, especially in women with white discharge per vaginam for early detection of intraepithelial neoplasia. Hence, there is need to strengthen the health services and programs for awareness. These screening programs are keys in reducing the burden of cervical cancer.

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Conflicts of interest

There are no conflicts of interest.

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