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Diagnostic Accuracy of Prostate Specific Antigen for the Detection of Malignancy in Breast Tumors Keeping Histopathology as Gold Standard

Ayesha Siddiqa[1], Nudrat Fayyaz[2], Afra Samad[2]*, Sara Khan[3], Faghia Shahid[4] and Tabinda Yasmeen[5]

[1] *District Health Authority, THQ Hospital, Yazman, Bahawalpur, Pakistan*

[2] *Department of Pathology, Multan Medical and Dental College, Multan, Pakistan*

[3] *Department of Pathology, CMH Institute of Medical Sciences, Bahawalpur, Pakistan*

[4] *Department of Pathology, SMDC, Lodhran, Pakistan*

[5] *Civil Hospital, Bahawalpur, Pakistan*

**Corresponding e-mail: themedresearcher@gmail.com*

ABSTRACT

Background/objective: *Breast cancer is a major concern worldwide and causes one of the highest numbers of causalities. The general approach for the evaluation of breast cancer has become formalized as triple assessment: clinical examination, imaging (usually mammography, ultrasonography, or both), and needle biopsy. Prostate-specific antigen (PSA) has been reported to be a potential biomarker of breast cancer. The objective of the present study was to determine the diagnostic accuracy of Prostate specific antigen for the detection of malignancy in breast tumors keeping histopathology as the gold standard.* ***Subjects and methods:*** *This cross-sectional study was conducted at the Department of Pathology, Quaid-e-Azam Medical College, Bahawalpur Victoria Hospital Bahawalpur from April 15, 2013, to October 14, 2013. All the patients with breast lump attending Surgery Outpatient Department were included in the study. Blood samples were collected in 5 ml sterile syringes on the same day before the FNAC was done. The total prostate-specific antigen of patients was assessed by commercially available ELISA kits and values >5 ng/L were labeled as positive.* ***Results:*** *Total of 230 patients were included in the study. The mean age of patients was 42 years with a standard deviation of 11.681 years. About 182 patients had breast cancer on histopathology while 160 patients were positive for PSA. PSA was found to be 78.2% precise in detection, the sensitivity of 80.2%, specificity of 70.8%, and positive predictive value of 91.2% and negative predictive value of 48.5%.* ***Conclusion:*** *Prostate specific antigen (PSA) has significant diagnostic accuracy in breast cancer and can be used as a diagnostic and prognostic marker of breast cancer in women.*

Keywords: Diagnostic accuracy, Prostate specific antigen, Breast tumors

INTRODUCTION

The prevalence of breast cancer has increased globally over the last several decades, the greatest increase in Asian countries. In Asia, breast cancer prevalence peaks among women in their 40s, whereas in the United States and Europe it peaks among women in their 60s. In India, premenopausal patients constitute about 50% of all patients. It is expected that in the coming decades, these countries would account for the majority of new breast cancer patients diagnosed globally. Over 100,000 new breast cancer patients are estimated to be diagnosed annually. Breast cancer cases are expected to increase by 26% by 2020 and most of these will be seen in developing countries [1].

There is 3.3% per year decrease in mortality in women aged 40-50 years suffering from breast cancer. Evaluation of mortality trends of breast cancer from 1990 through 2000 from 7 studies. The decrease in breast cancer (28% to 65%) is attributed to mammography screening, while the remaining of the decline was due to improved adjuvant treatments [2]. Breast cancer affects both men and women but; however, the prevalence is much higher in women.

Overall, women are at 100-fold higher risk of breast cancer than men. It is widely believed that breast tumors that are smaller or non-palpable and generally that present with a favorable tumor marker profile are more treatable if when detected early. A survival benefit of early detection with mammography screening has been demonstrated. A number of screening modalities exist for breast cancer, including clinical breast examination, mammography, ultrasonography, and MRI [3,4].

PSA is a single chain glycoprotein expressed at high levels in the epithelium of the human prostate gland. The prostatic function of PSA is to liquefy the sperm-entrapping seminal coagulum after ejaculation. The name "PSA" reflects the initial widespread belief that expression of the protein was restricted to the prostate gland. Over the past 5 years, however, this notion has clearly been dispelled. Numerous studies have shown that PSA is expressed in extraprostatic sites ally, suggesting that PSA may be functional outside the prostate gland. The peri-urethral (Skene's) gland was the first female tissue that was suggested to be able to produce PSA. This tissue has been referred to as the "female prostate because its developmental origin is homologous to that of the male prostate [5,6].

PSA is detectable in normal and hyperplastic breast tissue and is present in the majority of breast tumors and breast cysts. PSA is released into breast secretions, such as the milk of lactating women and nipple aspirate fluid. PSA gene expression in breast tumors appears to be under hormonal control because the steroid hormone receptor-positive breast cancer cell lines T-47D and BT-474 can be induced by androgens, progestins, mineral corticoids, and glucocorticoids to produce PSA *in vitro*. Detectable circulating levels of PSA, likely originating from breast tissue, are present in the serum of women. The PSA concentration in female sera is approximately 1000 fold less than that of males (0.004 mg/liter) [7].

Using chromatographic techniques it is found that the predominant form of PSA in the sera of women without breast cancer is PSA bound to ACT (serine protease inhibitor alfa 1 antichymotrypsin), whereas free PSA constitutes the major form of PSA in the pre-surgical serum of breast cancer patients. Level of serum PSA is affected by tumor size, lymph nodes involvement and patient received adjuvant therapy. Although free PSA as the predominant molecular form appears to be unique to breast carcinoma, an increase in total PSA levels in the serum of all breast cancer patients was observed in comparison to the control group. It is speculated that the slight increase in total PSA in the serum of women with breast cancer, benign breast disease, or uterine fibroids is the result of a disrupted hormonal balance in these women, triggering the aberrant expression of hormone-dependent genes such as PSA. The observation that total PSA is only slightly decreased in breast cancer patients after surgery is an indication that a major component of total PSA is not produced by the tumor cells but more likely by normal breast tissue [8]. The objective of the present study was to determine the diagnostic accuracy of Prostate specific antigen for the detection of malignancy in breast tumors keeping histopathology as the gold standard.

PATIENTS AND METHOD

This cross-sectional study was conducted at the Department of Pathology, Quaid-i-Azam Medical College, Bahawalpur Victoria Hospital Bahawalpur from April 15, 2013 to October 14, 2013. The current study was approved by the Institutional Ethical Review Committee.

Inclusion Criteria

Female patients of 15-75 years of age having a breast lump of $\geq$ 2 cm.

Exclusion Criteria

- Already diagnosed cases of breast cancer
- Acute infections in the previous 4-weeks

Data Collection Procedure

After the informed consent, all the patients with breast lump attending general surgery outpatient department of Quaid-e-Azam Medical College, Bahawalpur Victoria Hospital Bahawalpur were subjected to fine needle aspiration cytology (FNAC). FNAC of the breast tumor was performed by a senior surgeon. The samples of FNAC were examined for histopathological diagnosis of breast cancer. Breast carcinoma was labeled on the basis of pleomorphism, hyperchromatic nuclei, atypical bizarre mitotic figures, loss of polarity and presence of large tumors giant cells.

Blood samples were collected in 5 ml sterile syringes on the same day before the FNAC was done. Within 20 minutes

after collection, the samples were centrifuged at the rate of 3000 revolutions/minute for 10 minutes, and sera were separated and stored at -20ºC until assay. Total prostate-specific antigen was analyzed by ELISA in samples and values >5 ng/L were labeled as positive for prostate specific antigen.

Data Analysis Procedure

Data was entered and analyzed by SPSS version 14. Mean and the standard deviation was calculated for continuous variables like age. Frequency and percentage were calculated for a categorical variable such as positive PSA. A 2 × 2 table was used to calculate sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of PSA keeping histopathology as the gold standard. A p-value ≤ 0.05 was taken as statistically significant.

RESULTS

Total of 230 patients was included in the study. The mean age of patients was 42 years with a standard deviation of 11.681 years. The median age of patients was 40.50 years, minimum age of patients was 15 years, and the maximum age of patients was 65 years (Table 1 and Figure 1).

Table 1 Age statistics of patients in years

Total no patients (n)	**Valid**	**230**
	Missing	**0**
Mean age of patients in years		42
Median age of patients in years		40.5
Mode age of patients in years		35
Std. Deviation		11.681
Range age of patients in years		50
Minimum age of patients in years		15
Maximum age of patients in years		65

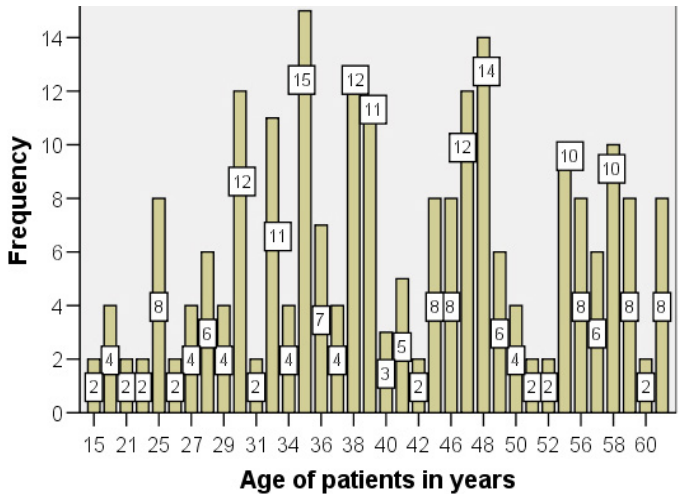

Figure 1 Distribution of patients according to age

Total 78 patients were in 15-35 years of age group, 112 patients were in 36-55 years of age group and 40 patients were in 56-75 years of age group (Figure 2).

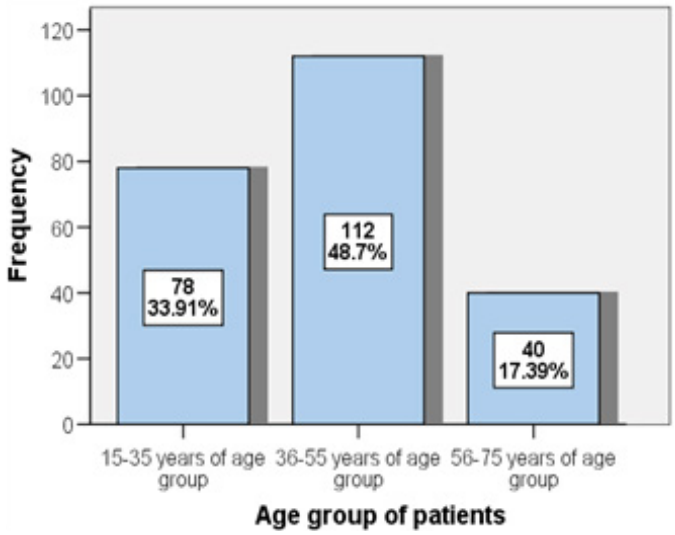

Figure 2 Patients in different age group

About 182 patients had breast cancer on histopathology and 48 patients had no breast cancer on histopathology (Figure 3).

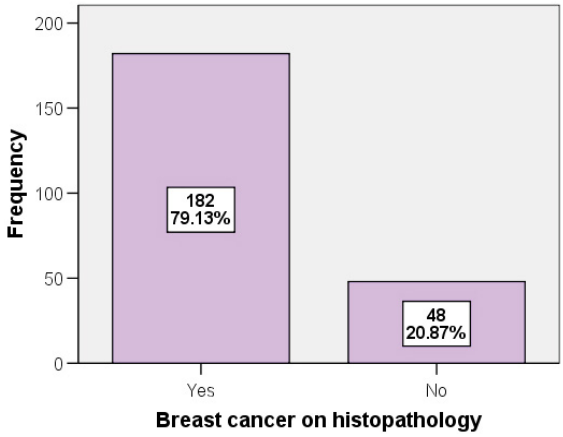

Figure 3 Breast cancer on histopathology

About 160 patients had breast cancer by measuring PSA while 70 patients had no breast cancer by measuring PSA (Figure 4).

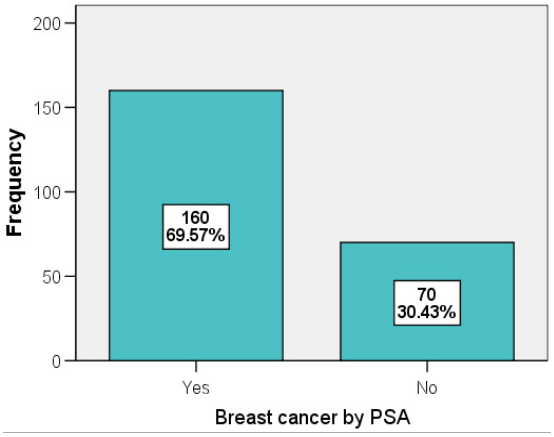

Figure 4 Breast cancer by PSA

On histopathology, 64 patients of 15-35 years of age group had breast cancer while 14 patients had no breast cancer, 88 patients of 36-55 years of age group had breast cancer while 24 patients had no breast cancer and 30 patients of 56-75 years of age group had breast cancer while 10 patients had no breast cancer with insignificant p-value of 0.658 (Table 2).

Table 2 Breast cancer on histopathology in the different age group of patients

Age group of patients (Years)	Breast cancer on histopathology		Total	p-value
	Yes	No		
15-35	64 (82.1%)	14 (17.9%)	78 (100.0%)	0.658
36-55	88 (78.6%)	24 (21.4%)	112 (100.0%)	
56-75	30 (75.0%)	10 (25.0%)	40 (100.0%)	
Total	182 (79.1%)	48 (20.9%)	230 (100.0%)	

By measuring PSA, 57 patients of 15-35 years of age group had breast cancer while 21 patients had no breast cancer, 79 patients of 36-55 years of age group had breast cancer while 33 patients had no breast cancer and 24 patients of 56-75 years of age group had breast cancer while 16 patients had no breast cancer with insignificant p-value of 0.327 (Table 3).

Table 3 Breast cancer by PSA in the different age group of patients

Age group of patients (Years)	Breast cancer by PSA		Total	p-value
	Yes	No		
15-35	57 (73.1%)	21 (26.9%)	78 (100.0%)	0.327
36-55	79 (70.5%)	33 (29.5%)	112 (100.0%)	
56-75	24 (60.0%)	16 (40.0%)	40 (100.0%)	
Total	160 (69.6%)	70 (30.4%)	230 (100.0%)	

The mean weight of patients was 68.94 kg with a standard deviation of 14.117 kg. The minimum weight of patients was 41 kg, maximum weight of patients was 95 kg (Table 4).

Table 4 Weight statistics of patients in kg

Total no of patients (n)	Valid	230
	Missing	0
Mean weight of patients in kg		68.940
Median weight of patients in kg		68.000
Mode weight of patients in kg		68.000
Std. Deviation		14.117
Range weight of patients in kg		54.000
Minimum weight of patients in kg		41.000
Maximum weight of patients in kg		95.000

On histopathology, 52 patients of 40-58 kg weight group had breast cancer while 16 patients had no breast cancer, 76 patients of 59-76 kg weight group had breast cancer while 20 patients had no breast cancer and 54 patients of 77-95 kg weight group had breast cancer while 12 patients had no breast cancer with insignificant p-value of 0.748 (Figure 5).

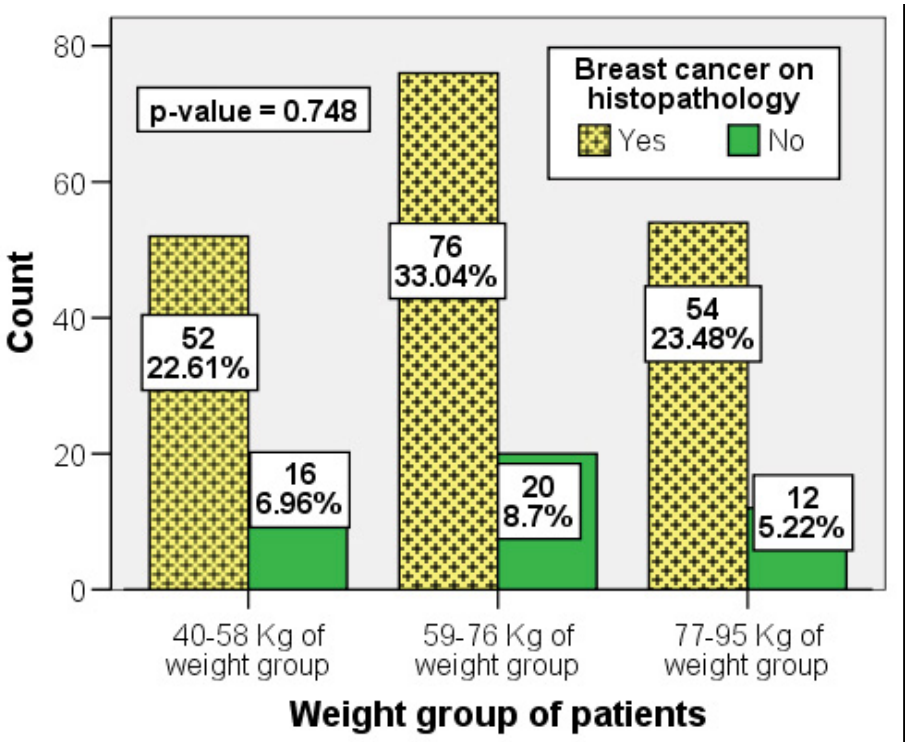

Figure 5 Breast cancer on histopathology in different weight groups of patients

By measuring PSA, 53 patients of 40-58 kg weight group had breast cancer while 15 patients had no breast cancer, 63 patients of 59-76 kg weight group had breast cancer while 33 patients had no breast cancer and 44 patients of 77-95 kg weight group had breast cancer while 22 patients had no breast cancer with insignificant p-value of 0.200 (Table 5).

Table 5 Breast cancer by PSA in different weight groups of patients

Weight group of patients (kg)	Breast cancer by PSA		Total	p-value
	Yes	No		
40-58	53 (77.9%)	15 (22.1%)	68 (100.0%)	0.2
59-76	63 (65.6%)	33 (34.4%)	96 (100.0%)	
77-95	44 (66.7%)	22 (33.3%)	66 (100.0%)	
Total	160 (69.6%)	70 (30.4%)	230 (100.0%)	

The diagnosing accuracy of PSA in detecting malignancy was 78.2%, with a sensitivity of 80.2%, specificity of 70.8%, the positive predictive value of 91.2% and negative predictive value of 48.5% (Table 6 and Figure 6).

Table 6 Showing the formula for calculating sensitivity, specificity, PPV and NPV of PSA in diagnosing breast cancer

Variables		Breast cancer on histopathology	
		Yes	No
Breast cancer by PSA	Yes	TP (125)	FP (29)
	No	FN (57)	TN (19)
TP: True positive, FP: False positive, FN: False negative, TN: True negative; Sensitivity: TP/TP+FN × 100; Specificity: TN/ TN+FP × 100; Positive Predictive Value: TP/TP+FP × 100; Negative predictive value: TN/FN+TN × 100; Diagnostic accuracy: TP+TN/ (TP+FP)+(FN+TN)			

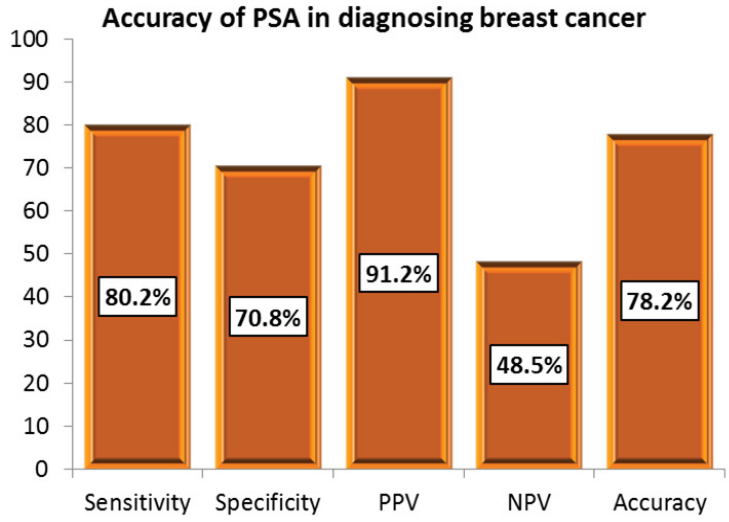

Figure 6 Sensitivity, specificity, PPV, NPV and accuracy of PSA in diagnosing breast cancer

Sensitivity, specificity, PPV, NPV, and accuracy of PSA in diagnosing breast cancer in different age groups (Tables 7-9).

Table 7 Sensitivity, specificity, PPV, NPV and accuracy of PSA in diagnosing breast cancer in 15-35 years of age group (n=78)

PSA	Histopathology		Total	p-value
	Positive	Negative		
Positive	True positive (a)	False positive (b)	a+b	0.138
	49 (62.8%)	8 (10.3%)	57 (73.1%)	
Negative	False negative (c)	True negative (d)	c+d	
	15 (19.2%)	6 (7.7%)	21 (26.9%)	
Total	a+c	b+d	78 (100%)	
	64 (82.1%)	14 (17.9%)		
Sensitivity=a/(a+c) × 100=76.56%; Specificity=d/(d+b) × 100=42.85%; Positive predictive value=a/(a+b) × 100=85.96%; Negative predictive value=d/(d+c) × 100=28.57%; Accuracy rate=a+d/(a+d+b+c) × 100=70.51%				

Table 8 Sensitivity, specificity, PPV, NPV and accuracy of PSA in diagnosing breast cancer in 36-55 years of age group (n=112)

PSA	Histopathology		Total	p-value
	Positive	Negative		
Positive	True positive (a)	False positive (b)	a+b	0
	74 (66.1%)	5 (4.5%)	79 (70.5%)	
Negative	False negative (c)	True negative (d)	c+d	
	14 (12.5%)	19 (17%)	33 (29.5%)	
Total	a+c	b+d	112 (100%)	
	88 (78.6%)	24 (21.4%)		
Sensitivity=a/(a+c) × 100=84.09%; Specificity=d/(d+b) × 100=79.16%; Positive predictive value=a/(a+b) × 100=93.67%; Negative predictive value=d/(d+c) × 100=57.57%; Accuracy rate=a+d/(a+d+b+c) × 100=83.03%				

Table 9 Sensitivity, specificity, PPV, NPV and accuracy of PSA in diagnosing breast cancer in 56-75 years of age group (n=40)

PSA	Histopathology		Total	p-value
	Positive	Negative		

Positive	True positive (a)	False positive (b)	a+b	0.000
	23 (57.5%)	1 (2.5%)	24 (60.0%)	
Negative	False negative (c)	True negative (d)	c+d	
	7 (17.5%)	9 (22.5%)	16 (40.0%)	
Total	a+c	b+d	40 (100.0%)	
	30 (75.0%)	10 (25.0%)		
Sensitivity=a/(a+c) × 100=76.66%; Specificity=d/(d+b) × 100=90%; Positive predictive value =a/(a+b) × 100=95.83%; Negative predictive value=d/(d+c) × 100=56.25%; Accuracy rate=a+d/(a+d+b+c) × 100=80%				

Sensitivity, specificity, PPV, NPV, and accuracy of PSA in diagnosing breast cancer in different weight groups (Tables 10-12).

Table 10 Sensitivity, specificity, PPV, NPV, and accuracy of PSA in diagnosing breast cancer in 40-58 kg of weight group (n=68)

PSA	Histopathology		Total	p-value
	Positive	Negative		
Positive	True positive (a)	False positive (b)	a+b	0.000
	46 (67.6%)	7 (10.3%)	53 (77.9%)	
Negative	False negative (c)	True negative (d)	c+d	
	6 (8.8%)	9 (13.2%)	15 (22.1%)	
Total	a+c	b+d	68 (100%)	
	52 (76.5%)	16 (23.5%)		
Sensitivity=a/(a+c) × 100=88.46%; Specificity=d/(d+b) × 100=56.23%; Positive predictive value=a/(a+b) × 100=86.79%; Negative predictive value=d/(d+c) × 100=60%; Accuracy rate=a+d/(a+d+b+c) × 100=80.88%				

Table 11 Sensitivity, specificity, PPV, NPV and accuracy of PSA in diagnosing breast cancer in 59-76 kg of weight group (n=96)

PSA	Histopathology		Total	p-value
	Positive	Negative		
Positive	True positive (a)	False positive (b)	a+b	0.000
	59 (61.5%)	4 (4.2%)	63 (65.6%)	
Negative	False negative (c)	True negative (d)	c+d	
	17 (17.7%)	16 (16.7%)	33 (34.4%)	
Total	a+c	b+d	96 (100%)	
	76 (77.21%)	20 (20.8%)		
Sensitivity=a/(a+c) × 100=76.63%; Specificity=d/(d+b) × 100=80%; Positive predictive value =a/(a+b) × 100=93.65%; Negative predictive value=d/(d+c) × 100=48.48%; Accuracy rate=a+d/(a+d+b+c) × 100=78.12%				

Table 12: Sensitivity, Specificity, PPV, NPV, and accuracy of PSA in diagnosing breast cancer in 77-95 Kg of weight group (n=66)

PSA	Histopathology		Total	p-value
	Positive	Negative		
Positive	True positive (a)	False positive (b)	a+b	0.001
	41 (62.1%)	3 (4.5%)	44 (66.7%)	
Negative	False negative (c)	True negative (d)	c+d	
	13 (19.7%)	9 (13.6%)	22 (33.3%)	
Total	a+c	b+d	66 (100%)	
	54 (81.8%)	12 (18.2%)		
Sensitivity=a/(a+c) × 100=75.92%; Specificity=d/(d+b) × 100=75%; Positive predictive value =a/(a+b) × 100=93.18%; Negative predictive value=d/(d+c) × 100=40.90%; Accuracy rate=a+d/(a+d+b+c) × 100=75.75%				

DISCUSSION

Breast cancer is a leading cause of morbidity and mortality in females of developed countries and is the most common malignancy among North American women. Currently, the most effective way to minimize morbidity and mortality from breast cancer is by early diagnosis and its treatment.

It is thus highly desirable to devise new methods for early diagnosis. Mammography is the most sensitive and specific screening modality for breast cancer; however, data presently available do not warrant a universal recommendation for mammography for all women [9,10].

Total PSA is one of the most valuable serum tumor markers, having been used successfully for diagnosis and postsurgical management of breast cancer. Use of PSA immunoassays for the management of breast cancer has resulted in a marked rise in the number of breast cancer detection. To further improve the effectiveness of distinguishing breast cancer from benign breast disease, measurement of various molecular forms of PSA has been introduced into clinical practice [11,12].

The mean age of patients in our study was 42 years with a standard deviation of 11.681 years and range age of patients was 15-65 years. The mean age of our patients was comparable to the mean age of patients in other studies. In a study conducted by Das, et al., showed that the mean age ± S.D of the study population was 46.6 years ± 9.55 years (standard deviation (S.D.)). The range was from 25 years to 66 years [13].

Our study showed sensitivity 80.2%, specificity 70.8%, positive predictive value 91.2%, negative predictive value 48.5% and diagnostic accuracy 78.2% of PSA. These results of our study were comparable to the results of other studies.

In another study conducted by Das, et al., showed that the total PSA was increased both in benign breast disease (86%) and breast cancer (70%) group in comparison to control group (33%) [13]. Serum-free PSA was also increased in both benign breast disease (28%) and breast cancer (38%). However, free PSA as the predominant form (that is when free PSA constituted more than 50% of total PSA) was specifically increased in breast cancer group (94%) in comparison with benign breast disease group (24%). It was also found that total PSA had good sensitivity (70%) but low specificity (25%). Free PSA was specific (90%) but not that sensitive (40%), whereas free PSA, as the predominant form was both sensitive (94.84%) and specific (97%). Serum PSA was found to be decreased after surgery. A significant decrease (>90% of the pre-surgery value) was seen in 78% cases. Moderate decrease (50%-90% of the pre-surgery value) was found in 12% cases. Minimal decrease (<50% of pre-surgery value) was seen only in 7% cases. Very few cases (3%) showed no decrease after surgery. A study conducted by Chang, et al., showed that In clinical serum samples, moreover, the experimental results of total PSA detection show that both the mean value and median in the breast cancer group (155.2 and 145.7, respectively) are higher than those in the non-cancer group (46.6 and 37.1, respectively) [14-16].

A study conducted by Fawzi, et al., showed that total and free PSA levels were significantly higher in women with breast cancer (preoperatively) than in healthy women ($p<0.001$) [17]. Both serum total PSA and free PSA showed a significant decline in their pre-surgical values after surgical removal of the tumor. In another study, Ukinc, et al., achieved cut off point of PSA level for diagnosis greater than 10 pg/ml which yielded sensitivity and specificity of 73.2% and 80%, respectively, whereas cut-off point of FPSA level for diagnosis of PCOS greater than 2.1 pg/ml yielded sensitivity of 85.4% and specificity of 80.4% [18]. Prostate specific antigen (PSA) is a well-established tumor marker for the diagnosis and management of prostate cancer. With the advent of more sensitive methodologies for PSA detection, it is found that PSA is not prostate specific, but is present in female tissues, predominantly the breast and its secretions. Since the initial discovery of PSA in females, numerous normal and pathological tissues and body fluids have been reported to have PSA immunoreactivity. PSA is detectable in healthy breast tissue and is present in breast tumors and breast cystic disease.

CONCLUSION

Nevertheless, our findings of serum PSA in breast tumor suggest that PSA can no longer be regarded as a specific prostatic marker. However, it can be used to distinguish between healthy women and/or women with advanced breast cancer. Prostate specific antigen (PSA) has significant diagnostic accuracy in breast cancer in our study and can be used as a diagnostic and prognostic marker of breast cancer in women. Clinical applicability of prostate specific antigen for breast cancer diagnosis and the biological mechanism behind its increase should be further investigated.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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