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The impact of Tumor markers (CEA and Resistin) and *RETN* gene polymorphism (rs10401670 T/C) in Iraqi BC patients

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Abstract

Background. Carcinoembryonic antigen (CEA) is one of the initial tumor biomarkers to be characterized and recognized. Resistins are 12-kDa cystine-rich polypeptide hormones proteins released via adipocytes and macrophages in mice and humans, respectively. The diagnostic role of these two markers has not been deeply investigated in published Iraqi literatures. **Aim.** Determination of Resistin and CEA concentration by ELISA and molecular analysis for *RETN* single nucleotide polymorphisms SNPs rs10401670 T/C in BC patient Patients and methods: Methods. These study included100 BC patients who attended Al- Amal Hospital / Baghdad/Iraq, for the period from June 2023 to October 2023. The study's experimental work was performed in the Institute for Genetic Engineering and Biotechnology for postgraduate studies / University of Baghdad, laboratories of Al- Amal Hospital, as well as the private medical laboratories. 100 apparently healthy women were matched in age with BC patients were included. Serum measurement of CEA and Resistin were done using ELISA. The molecular analysis for *RETN* single nucleotide polymorphisms SNPs included rs10401670 T/C**. Results:** Serum levels (median (IQR)) of Carcinoembryonic antigen (CEA) were higher significantly in BC group in comparisons with HCs, 104.05 pg/ml *versus* 26.85 pg/ml, respectively ($p< 0.001$). Serum levels (median (IQR)) of Resistin (RETN) were higher significantly in BC group in comparisons with HCs, 1.16 ng/ml *versus* 0.41 ng/ml, respectively ($p< 0.001$). The cutoff value of CEA was >35.71 (pg/ml) with an area under curve (AUC) of > 0.7 (0.762) indicating good accuracy level of 76.2 %; the sensitivity was 69.7 % and the specificity was 79.2 %. The cutoff value of *RETN* was >0.41 (ng/ml) with an area under curve (AUC) of > 0.7 (0.742) indicating good accuracy level of 74.2 %; the sensitivity was 89.9 % and the specificity was 51.5 %. Comparisons of *RETN* (rs10401670 T/C) genotypes and alleles between patients with BC and HCs revealed that TC and CC genotypes had significant association with BC ($p< 0.001$ and $p < 0.001$, respectively); the ratio of TC and CC genotypes were higher in patients in comparisons with HCs, 53 *versus* 34 and 25 *versus* 10, respectively, therefore both of them acts as a risk factor with odds ratios of 3.97 (2.06 -7.64) and 6.36 (2.63 -15.40), respectively. **Conclusion.** Both serum CEA and *RETN* levels can provide adjuvant diagnostic role in BC and use of combination of both markers will increase their accuracy in this regard. *RETN* (rs10401670 T/C) has significant impact on risk of cancer.

Key words: CEA, Resistin, breast, cancer

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Introduction

The global impact of BC on public health is substantial. Comprising 23% of all female malignancies, it is far more prevalent than any other kind of cancer in women. Approximately 1.15 million new instances of BC were reported in 2002, with 411,000 deaths being directly attributable to this illness (1). Cancer of breast is the most prevalent tumor in females worldwide and the second most prevalent tumor generally. Worldwide, it is the most common cancer in women, and it is curable in 70–80% of cases when caught early and not spread to other parts of the body (2). With the treatments that are available today, advanced BC that has spread to other organs is deemed incurable. BC is a complex illness with a wide range of molecular characteristics.

Some of these aspects include HER2 activation, hormone receptor activation (both estrogen and progesterone receptors), and BRCA mutations (3). It includes a group of molecularly and biologically heterogeneous illness created from a breast (4). It is an unrestrained growth of epithelial cells creating in the lobules of breast or ducts (5). An early tumor marker that was discovered and studied was carcino-embryonic antigen (CEA). For many years after its discovery, CEA served as the gold standard for evaluating novel blood markers in a variety of cancers, including cancer of breast. According to many studies, elevated blood CEA levels at first BC diagnosis may be a poor prognostic indicator that correlates with disease stage. The state of disease development or regression may be indicated by a rise or reduction in the CEA levels, according to some experts (6).

Human macrophages and mouse adipocytes release the hormone protein resistin, which is rich in cysteine and has a 12 kDa-molecular weight. It has 108 amino acid peptides and is the progenitor of the hormone family of resistin-like molecule (RELM). In humans, it circulates as a dimer of two polypeptides of 92-amino acids. Locations 3'-untranslated and the *retn* promoter have single nucleotide polymorphisms. Multiple illnesses, including BC, metabolic syndrome, and colon cancer, are associated with *retn* locus genetic polymorphism (7; 8).

Genotyping for single nucleotide polymorphisms (SNPs) may help improve BC risk prediction and treatment (9; 10). BC susceptibility is affected by certain SNPs (11).

Patients and Methods

This study included 100 BC patients who attended Al- Amal Hospital / Baghdad/Iraq, for the period from June 2023 to October 2023. The study's experimental work was carried out in the Institute for Genetic Engineering and Biotechnology for postgraduate studies / University of Baghdad, laboratories of Al- Amal Hospital, as well as the private medical laboratories. Females older than 20 years with definitive diagnosis of BC based on clinical examination, radiologic imaging and histopathology reports. Patients on treatment and patients with other malignancy or comorbidity were excluded from the study. 100 apparently healthy women were matched in age with BC. Venous blood (3 ml) was collected from each subject and then centrifuged to isolate the serum to measure the CEA and Resistin concentration in BC patients. CEA is a tumor markers were measured by using a kit according to ELK (Wuhan) Biotechnology CO., Ltd.Cat: ELK026ES. *Retn* is a tumor markers were measured by using a kit according to ELK (Wuhan) Biotechnology CO., Ltd.Cat: ELK1225.

Genotyping was determined by extraction DNA from the samples then

subjected to the polymerase chain reaction (PCR) followed by DNA sequencing and sequence analysis. Agarose gel electrophoresis was used to validate the existence of amplification after PCR amplification. The extracted DNA criteria were the only determinant of PCR's reliability. The molecular analysis for *RETN* single nucleotide polymorphisms SNPs included rs10401670 T/C. Macrogen Company provided the lyophilised primers, which were created using the NCBI-BLAST primer creation program.

Results Comparisons of serum markers between BC groups and HCs is shown in table 1 and figure 1. Serum levels (median (IQR)) of Carcinoembryonic antigen (CEA) were higher significantly in BC group in comparisons with HCs, 104.05 pg/ml *versus* 26.85 pg/ml, respectively ($p< 0.001$). As in table 1 and figure 2, serum levels (median (IQR)) of Resistin (RETN) were significantly higher in BC group in comparisons with HCs, 1.16 ng/ml *versus* 0.41 ng/ml, respectively ($p< 0.001$). In this study, serum levels of CEA in patients with BC averaged 104.05 pg/ml and it was significantly higher in BC group in comparisons with HCs.

Table 1: Comparisons of serum markers between BC groups and HCs

Characteristic	BC group *n* = 100	HCs *n* = 100	*p*
CEA (pg/mL)			
Median (IQR)	104.05 (261.24)	26.85 (16.47)	< 0.001 M ***
Range	0.48 -559.76	10.91 -191.67	
***RETN* (ng/mL)**			
Median (IQR)	1.16 (1.46)	0.41 (0.99)	< 0.001 M ***
Range	0.06 -6.38	0.02 -1.7	

CEA: carcinoembryonic antigen**; RETN:** resistin; ***: significant at $p \leq 0.001$; **M**: Mann Whitney U test; **IQR**: inter-quartile range; ***n***: number of cases.

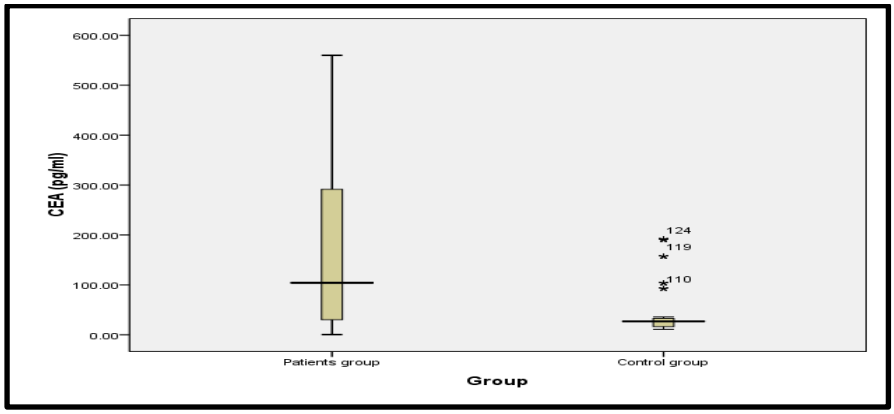

Figure 1: Plot box representing comparisons of sera' CEA between BC group and HCs

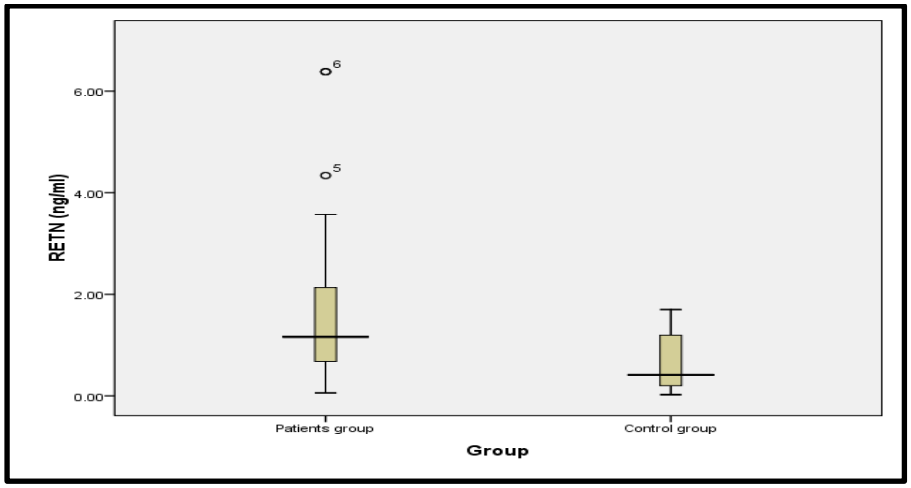

Figure 2: Plot box representing comparisons of sera *RETN* among BC group and controls' group

In this study also, with respect to CEA, there was significant positive correlation with age and significant negative correlation with location of tumor (higher levels with right sided lesion and lower levels with left sided lesion), as shown in table 2. Correlations of CEA, and *RETN* to clinicpathological characteristics of patients with breast carcinoma are shown in Table 2. With respect to CEA, there was significant positive correlation with age and significant negative correlation with location of tumor (higher levels with right sided lesion and lower levels with left sided lesion). With respect to RETN, there was significant positive correlation with grade of tumor and ER expression and significant negative correlation with family history. Receiver Operating Characteristic (ROC) analysis was conducted to delineate the predictive role of CEA levels in metastasis among BC patients, establishing a cut-off value of 1.39 ng/ml. The sensitivity of CEA levels was determined to be 88.3% with a specificity of 46.2%. Within our own research, the identified CEA cut-off value was >35.71 (pg/ml) with an accuracy rate of 76.2%; sensitivity measured at 69.7% and specificity at 79.2%, as shown in figure (3) and table (3). The diagnostic potential of serum CEA and serum *RETN* in case of BC was evaluated using receiver operating characteristic (ROC) curve analysis and the results were shown in Table 3 and Figures 3 and 4. The cutoff value of CEA was >35.71 (pg/ml) with an area under curve (AUC) of > 0.7 (0.762) indicating good accuracy level of 76.2 %; the sensitivity was 69.7 % and the specificity was 79.2 %.The cutoff value of *RETN* was >0.41 (ng/ml) with an area under curve (AUC) of > 0.7 (0.742) indicating good accuracy level of 74.2 %; the sensitivity was 89.9 % and the specificity was 51.5 %. In our study, we tested the diagnostic potential of resistin and we reported that the cutoff value of *RETN* was >0.41 (ng/ml) with accuracy level of 74.2 %; the sensitivity was 89.9 % and the specificity was 51.5 % (as shown in figure 4).

Table 2: Correlations of CEA, and *RETN* to clinicopathological characteristics of patients with breast carcinoma

Characteristic	CEA (pg/ml)		*RETN* (ng/ml)	
	r	***p***	***r***	***p***
Age	0.226	0.024 *	0.094	0.351
Grade	0.180	0.074	0.293	0.003 **
Tumor size	-0.179	0.075	-0.094	0.350
Lymph node	0.000	0.994	-0.105	0.301
Metastasis	0.059	0.559	0.061	0.544
Family history	-0.132	0.190	-0.313	0.001 **
Type of BC	0.136	0.177	-0.017	0.867
Location of BC 1= Left, 2= Right, 3= Bilateral	-0.326	0.001 ***	-0.182	0.070
ER	0.008	0.934	0.199	0.047 *
PR	-0.120	0.234	-0.170	0.090
HER2	-0.111	0.271	0.000	1.000

*: significant at $p \leq 0.05$; **CEA:** carcinoembryonic antigen**; RETN:** resistin; ***: significant at $p \leq 0.001$; **PR**: progesterone; **ER**: estrogen receptors; **BC**: BC; **: significant at $p \leq 0.01$.

Table 3: The diagnostic potential of serum CEA and serum *RETN* in case of BC

Characteristic	CEA	RETN
Cutoff	>35.71	> 0.41
AUC (95 % CI)	0.762 (0.697 to 0.820)	0.742 (0.676 to 0.801)
p	<0.001***	<0.001***
Sensitivity %	69.7	89.9
Specificity %	79.2	51.5
Accuracy %	76.2	74.2

CEA: carcinoembryonic antigen; **AUC**: area under curve; **RETN**: resistin;

CI: confidence interval; ***: significant at $p \leq 0.001$.

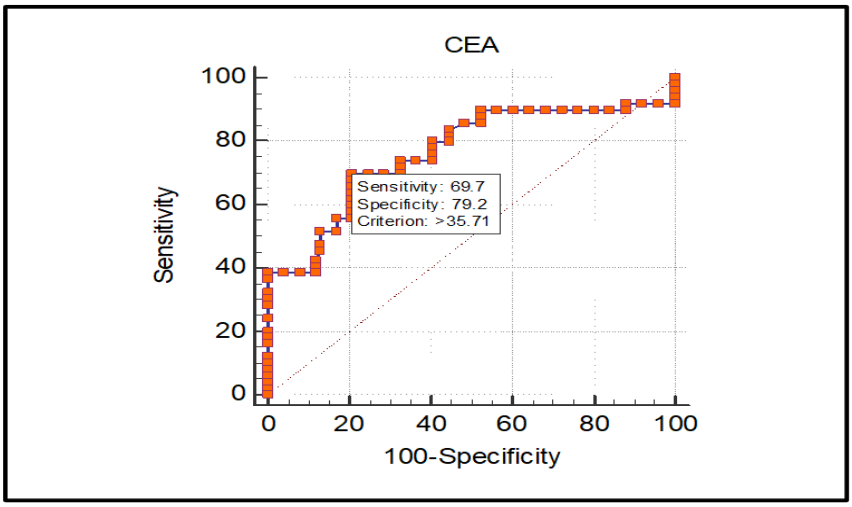

Figure 3: Curve analysis of receiver operating characteristic (ROC) to indicate the value of cutoff of serum CEA level that can predict a diagnosis of breast carcinoma with best accuracy

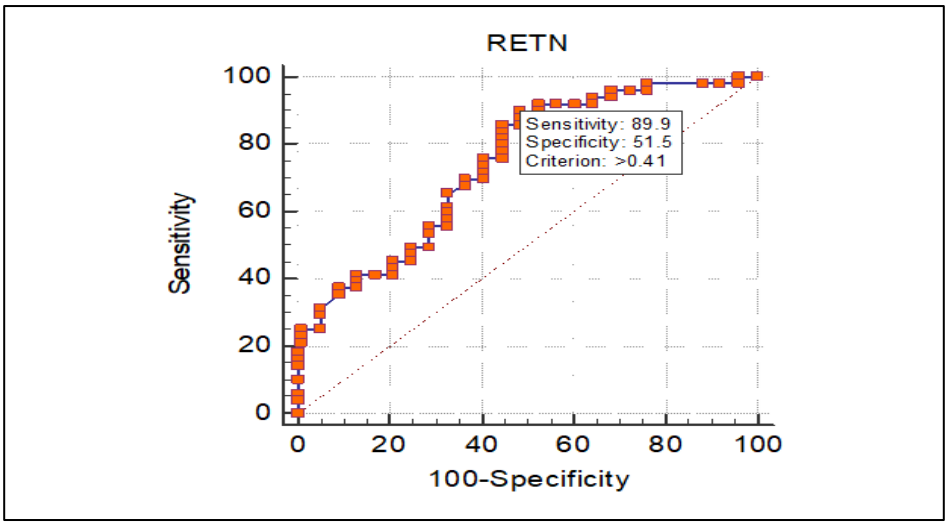

Figure 4: Curve analysis of receiver operating characteristic (ROC) to indicate the value of cutoff of serum resistin (RETN) level that can predict a diagnosis of breast carcinoma with best accuracy

Figure 5 showed the molecular weight of DNA bands (706 bp) of *rs10401670 SNP* for *RETN* gene of patients after amplification by PCR. The Hardy Weinberg equilibrium showed non- significant variations in total cases and in patients and HCs as shown in Table 4. Regarding all enrolled cases, TT genotype was seen in 78 subjects, TC genotype was observed in 87 subjects and CC genotype was seen in 35 subjects. Regarding BC group, TT genotype was seen in 22 subjects, TC genotype was observed in 53 subjects and CC genotype was seen in 25 subjects. Regarding HCs, TT genotype was seen in 56 subjects, TC genotype was observed in 34 subjects and CC genotype was seen in 10 subjects.

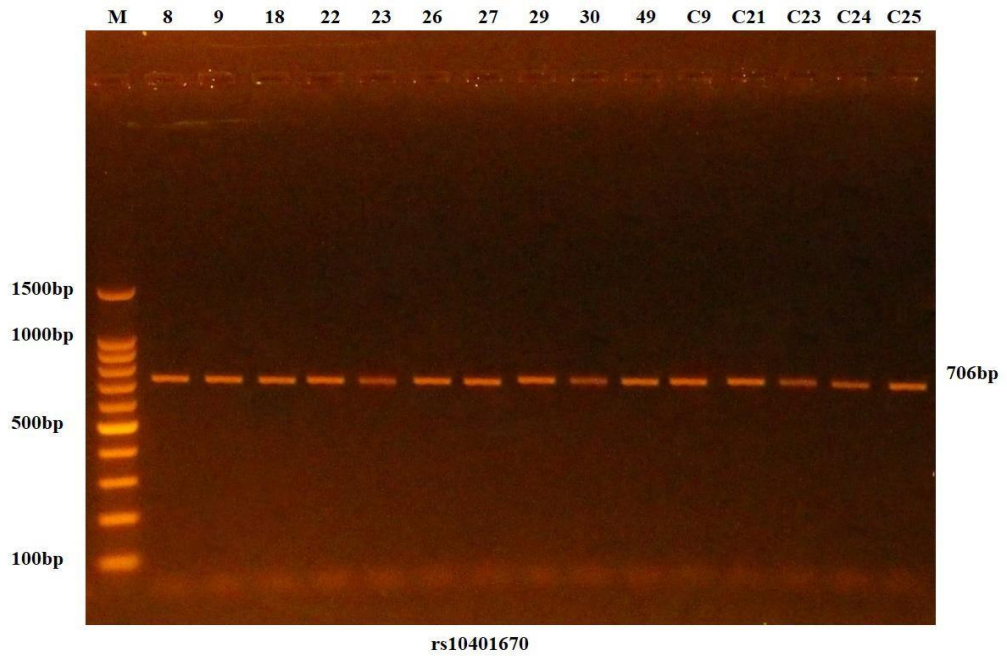

Figure 5: The molecular weight of DNA bands(706 bp)of of*rs10401670 SNP* for *RETN* gene of patients after amplification by PCR and these bands were checked under the UV-light after staining with the red safe on (2%) of agarose gel at (75 volt for 1.30 hour). Lane M: ladder of DNA (100 bp). Lane (1-15): BC patients

Table 4: The Hardy Weinberg equilibrium in total cases and in patients and HCs

RETN **(rs10401670 T/C)**	**Total** ***n*** **= 200**		**BC group** ***n*** **= 100**		**HCs** ***n*** **= 100**	
	Observed count	**Expected count**	**Observed count**	**Expected count**	**Observed count**	**Expected count**
TT	78	73.8	22	23.5	56	53.3
TC	87	95.4	53	50.0	34	39.4
CC	35	30.8	25	26.5	10	7.3
χ^2	1.543		0.372		1.890	
p	0.214 NS		0.542 NS		0.169 NS	

RETN: resistin; ***: significant at $p \leq 0.001$; **NS:** not significant.

Comparisons of *RETN* (rs10401670 T/C) genotypes and alleles between patients with BC and HCs is shown in Table 5. With respect to co dominant model, TT genotype was considered as a reference, and both TC and CC genotypes showed significant association with BC ($p < 0.001$ and $p < 0.001$, respectively); the rates of TC and CC genotypes were higher in patients in comparisons with HCs, 53 *versus* 34 and 25 *versus* 10, respectively, therefore both of them acts as a risk factors with odds ratios of 3.97 (2.06 -7.64) and 6.36 (2.63 -15.40), respectively. In the dominant model, TT genotype was significant protective factor against BC ($p < 0.001$) with a ratio of

odds(95% CI)of 0.22 (0.12 -0.41); whereas, in the recessive model, CC genotype was significant risk factor ($p< 0.001$) with a ratio of odds of 3.00 (1.35 -6.64). Allele analysis revealed that allele T was significant protector ($p< 0.001$) with a ratio of odds of 0.35 (0.23 -0.53) and allele C was significant risk factor ($p< 0.001$) with a ratio of odds of 2.87 (1.89 -4.36).

Table 5: Comparisons of *RETN* (rs10401670 T/C) genotypes and alleles frequency between BC patients and group of controls

Models	*RETN* (rs10401670 T/C)	BC group *n* = 100	HCs *n* = 100	*p*	OR (95% CI)
Co-dominance	TT	22	56	Reference	Reference
	TC	53	34	< 0.001 C ***	3.97 (2.06 -7.64)
	CC	25	10	< 0.001 C ***	6.36 (2.63 -15.40)
Dominant	TT	22	56	< 0.001 C ***	0.22 (0.12 -0.41)
	TC+CC	78	44	Reference	Reference
Recessive	CC	25	10	0.005 C **	3.00 (1.35 -6.64)
	TT+TC	75	90	Reference	Reference
Allele	T	97	146	< 0.001 C ***	0.35 (0.23 -0.53)
	C	103	54		2.87 (1.89 -4.36)

CI: confidence interval; **OR**: odds ratio; NS: not significant; **C**: chi-square test; ***n***: number of cases; **: significant at $p \leq 0.01$;

Discussion

Metastatic and recurring BCs are associated with significantly higher blood CEA levels in patients. Serum CEA positive rates have been reported in investigations ranging from 36% to 70% (10). These heightened levels are recognized to exhibit a positive correlation with tumor burden, tumor grade, and metastatic site, consequently leading to decreased overall survival (OS) and progression-free survival (12). The recommendation for serial monitoring of tumor markers is not supported for asymptomatic individuals post BC treatment (13; 14). The primary use lies in the monitoring of metastatic disease progression during treatment, particularly focusing on CA15-3. Commonly used markers of tumor of sera in cancer of breast are CEA and CA15-3 (15; 16). Therefore, the estimation of serum CEA can be considered as an adjunctive method for evaluating treatment response, monitoring progress, and obtaining prognostic insights. Nevertheless, the clinical applicability of these markers remains uncertain due to conflicting outcomes (17; 18). In the investigation by (19).In the present study, serum levels of *RETN* (median (IQR))1.16 ng/ml and it was significantly higher in BC group in comparisons with group of control as shown in Table 3. Indeed, the conclusions of a number of prior papers

(20; 21; 22) are consistent with the results of this work. The investigation conducted by (20) involved the collection of blood samples from 80 recently diagnosed BC patients who had received histological confirmation, along with 50 age-matched healthy controls. The findings indicated that the serum values of resistin were raised in HC cases in comparisons to the BC group, with levels of (23.32±4.75) µg/L v*ersus* (26.35±5.36) µg/L, showing a statistically significant variation (p=0.000). In the research by (21)), it was observed that the average levels of sera' resistin were notably higher in the cases as opposed into the group of control (p<0.001). Furthermore, in the study conducted by (22), a cohort of 82 newly diagnosed BC patients who had histological confirmation and 68 healthy HCs matched in terms of BMI and age were included. The results revealed significantly elevated levels of resistin in cancer of breast patients in comparisons with their respective control counterparts. There was no significant variation in sera values of resistin among BC and HC groups (p=0.064), as stated in the results of (23) which contradicted the present study's findings. The women with breast carcinoma were found to have levels of resistin of 6.11 ± 4.49 ng/ml, while the control subjects had an average level of 6.14 ± 1.83 ng/ml. The present study's results are consistent with those of resistin, which showed poor diagnostic performance according to ROC curve analysis, with a total accuracy level of 72% (21). According to a number of scientific studies, resistin is essential for cancer cell metabolic regulation, angiogenesis, inflammation, proliferation, and metastasis (8). Resistin may serve as a biomarker for BC that indicates a state of inflammation and progressive stage of illness, even if its diagnostic performance was poor according to analysis of curve of ROC (0.72, 95% CI: 0.64-0.79) (21).Resistin is a biomarker that may help with early diagnosis and understanding the treatment regimen for any illness since it is a quantifiable feature of the patho-physiological state of a person (21). There is mounting evidence that resistin might be a valuable biomarker for cancer prognosis and diagnosis (20). Research involving 80 women with cancer of breast and fifty healthy controls found that the patients of cancer had higher resistin levels than the HCs. Furthermore, it was shown that individuals with lymph node metastases had a higher resistin level compared to those without this disease (24). Retin levels are related into an BC advanced risk, regardless of body mass index (BMI), glucose of blood, menopausal status, age, or adiponectin. But it's linked to lymph node invasion, tumor size, cancer grade, stage, inflammation, and tumor and inflammatory markers (21; 22**)**. (20) documented that the serum concentrations of resistin exhibited notable discrepancies between individuals afflicted with lymph node metastasis and those devoid of such metastasis. Concurrently, (21) noted in their study that resistin displayed a significant correlation with various parameters in BC patients, including cancer stage, tumor dimensions, grade, and lymph node infiltration, while exhibiting no apparent association with hormone receptor status. Serum resistin levels are positively linked with histological grading, metastasis of lymph nodes, tumor size, and TNM (metastasis, lymph node and tumor size) staging, according to Assiri *et al.* (22**)**. Our study found a robust negative links among RETN and family medical history, and a strong positive link with tumor grade and ER expression. In this study, for the second SNP, the Hardy Weinberg equilibrium in groups of controls and patients displayed no significant variations among expected and observed counts; however, genotype and allele analysis revealed that genotypes TC and CC and allele C were risk factors for BC and that TT genotype and allele T were protective factor

against BC. In addition, this study reported that no significant association between genotypes and clinic-pathological characteristics or tumor markers serum levels. Following extended search in available published article in internet database, the researcher failed to a find an article linking gene polymorphism of *RETN* (rs10401670 T/C) SNP to BC; therefore, and to the best of our knowledge, this is the first research effort to link such SNP gene polymorphism of *RETN* gene with risk and incidence of BC and this is a point of originality in this thesis. However, Deng *et al*. (2020) published an article about the possible association between *RETN* (rs10401670 T/C) SNP and bladder cancer and found that CT/TT genotype and allele T of rs10401670 is linked with reduced occurrence of cancer of bladder.

Conclusion

Both serum CEA and *RETN* levels can provide adjuvant diagnostic role in BC and use of combination of both markers will increase their accuracy in this regard. *RETN* (rs10401670 T/C) has significant impact on risk of cancer.

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