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Association Between Sirtuin1 (SIRT1) Gene Polymorphism and Breast Cancer

Raghad Abdel-Salam Mostafa Ibrahem [1], Gihan Farouk Attia [1], Samar Galal Younes [2], Ghada Abd El mo'men Soliman [1], Mona Mohamed watany [1]
[1] *Clinical Pathology, Faculty of Medicine, Tanta University, Tanta, Egypt*
[2] *Clinical Oncology, Faculty of Medicine, Tanta University, Tanta, Egypt*

ABSTRACT
Background
Breast cancer is one of the most prevalent causes of cancer mortality among women, with over 1 million new cases identified each year, being responsible for 90% of fatalities due to metastasis to distant sites. The aim of this study is to study the role of SIRT1 gene polymorphism in breast cancer.
Subjects and Methods
The present study was carried on 75 female human subjects, divided into two groups; one include 50 female recently diagnosed with breast cancer (Group I) and another 25 normal healthy female free of breast cancer as control group (Group II). ***Screening of SIRT1 gene single nucleotide polymorphisms using real-time PCR and*** *serum level of SIRT1 using ELISA technique were evaluated.*
Results
SIRT1 levels were increased in breast cancer patients compared to control group and varied in study groups according to tumor staging and lymph node infiltration. There was an association between SIRT1 gene polymorphism (rs3758391) and breast cancer risk, with the T allele being a risk factor.
Conclusion
On basis of these results, it could be concluded that, combination of SIRT1 inhibitors and estrogen antagonisit may represent more effective treatment for breast cancer as a part of treatment strategy.
Keywords: *SIRT1, polymorphism and breast cancer.*

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I. INTRODUCTION

Breast cancer is an aggressive disease and reported as the highest incidence of malignancy-rated deaths among women worldwide (1). It is a multifactorial genetic disease, including, inheritance and hormonal disorder (2). Despite much improvement in diagnostic technique and treatment, the 5-year survival rate is still unsatisfactory (3).

Since breast cancer is a complex, there is a need for effective therapies (4, 5).

Breast cancer pathogenesis of is multifactorial and the relation between SIRT1 expression with the clinical picture and the outcome is not been fully understood.

Sirtuin 1 (SIRT1) is one member of the sirtuin family seven members; of nicotinamide adenine dinucleotide (NAD+)-dependent class III histone deacetylase (6).

Sirtuin 1 mediates the deacetylation of various substrates including forkhead box class O (FOXO), p53 and other proteins, and thus regulates different biological processes including aging, metabolism and genomic stability and (7).

SIRT1 misregulation is involved biochemically and genetically in diseases as diabetes mellitus and has been introduced as a therapeutic agent in osteoarthritis, neurodegeneration and cardiovascular disease (7).

Increased expression of SIRT1 has been reported in various human malignancies other than breast cancer, including prostate cancer, myeloid leukemia, and cancer colon (8).

The apparent controversy roles of SIRT1 seem opposed but the multiple functions of SIRT1 can explain it. SIRT1 negatively regulate many pathways including both tumor suppressors (p53, FOXO) and oncogenic proteins (β-catenin, NF-κB) (9).

SIRT1 suppress tumorigenesis. However, SIRT1 regulates cellular pathways to promote proliferation, progression of tumors and genetic/ epigenetic changes (10).

II. SUBJECTS AND METHODS

Subjects:

This study was carried out on 75 female human subjects; 50 female individuals recently diagnosed with breast cancer, selected from clinical Oncology Department, Tanta University Hospital (Group I). Another 25 healthy subjects, matched for age were included as a control group (Group II).

All individuals included in this study were subjected to the following:

- Detailed history taking including personal, reproductive and family history.
- Thorough clinical examination with particular attention to organomegaly, L.Ns enlargement and any other masses.
- Mammography.
- Clinical staging (TNM), histological grading of the tumor and immunohistochemical study of estrogen receptor (ER), progesterone receptor (PR), collected from the patients' files.

Specific laboratory investigations:

1. Screening of SIRT1 gene single nucleotide Polymorphisms using real-time PCR.
2. Serum level of SIRT1 using ELISA technique.

Specimen:

Blood collection was performed under sterile conditions. Blood samples (5 mL) were collected into vaccutainer tubes, about 3ml of them were collected in plain tube then centrifuged, sera samples were stored at -20°C till the time of SIRT1 measurement. The remaining 2ml of blood were collected in EDTA vacutainer tube & stored at -20°C for molecular investigation.

Methods:

I) Measurement of serum level of SIRT1:

Using commercial Enzyme-linked Immunosorbent Assay Kit For the quantitative detection of SIRT1, supplied by clini-lab catalog no: MBS2503120.

II) Detection of (SIRT1) rs 3758391 gene polymorphism:

- SNP rs**3758391** of mammalian silent information regulator-two 1 (SIRT1) gene determined by using real time PCR (Applied bio system, step I version). Specific-sequence to amplify (the sequence of interest (rs) 3758391)

✓ Forward prime rs 3758391F: TGCTGGCCTAATAGAGTGGCA
✓ Reverse primer rs 3758391R: CTCAGCGCCATGGAAAATGT

The run was completed on real-time PCR System (Applied biosystem, step I version) using the following thermal cycles: 50°C for 2 min, 95°C for 10 min and 40 repetitions of 95°C for 15 s and 60°C for 1 min.

Analysis of the result:

After the experiment was completed, the experiment data were saved and applied biosystem, step I version Software analysis modules were used to evaluate the results.

Statistical analysis

Using the SPSS software statistical computer programme version 12, the acquired data was organised, tabulated, and statistically evaluated. The range, mean, and standard deviation were determined for quantitative data. The number and % of distribution were computed using qualitative data. The Chi-square test was performed to determine significance. The significance level was set at 0.05 [(11)]**.**

III. RESULTS

As shown in table 1 a statistically significant difference between the groups regarding the genotype SIRT1 (rs3758391) distribution. The percentage of TT and CT genotypes was higher in breast cancer group than controls. While, the percentage of CC genotype was significantly lower in breast cancer group than the controls.

There was a statistically significant difference between the studied groups regarding the SIRT1 allele frequency, the percentage of the T allele was higher in BC group compared to control group. While, the percentage of C allele was significantly lower in breast cancer group than controls as shown in table 2.

Table 3 shows that SIRT1 serum levels in BC group was significantly higher as compared to the controls. Moreover serum SIRT1 levels were significantly higher in BC patients with CT and TT genotypes than those with CC genotype (table 4).

Table 5 shows a positive correlation between SIRT1 levels with tumor grade (r=0.447, p= 0.001*), size (r=0.533, p= 0.001*), lymph nodes N infiltration (r= 0.477, p= 0.001*), estrogen receptor (r= 0.400, p= 0.004*) progesterone receptor (r= 0.305, p= 0.031*)

IV. DISCUSSION

Breast cancer is one of the commonest causes of cancer death rate in women, with huge new cases diagnosed each year, being responsible for 90% of fatalities due to metastasis to distant sites [(12)].

The SIRT1 is a well studied member of sirtuins family, it is a type III histone deacetylase, and has been recorded to have both pro- and anti-carcinogenic effect in various human cancers, including breast cancer [(13, 14)]. This study tried to explore SIRT1 role in development and progression of breast cancer, as well as the associated mechanisms of action.

Regarding the genotype variants of SIRT-1 (rs3758391) distribution. This current study showed that the percentage of TT and CT genotypes were higher in breast cancer patients than the control groups. While, the percentage of CC genotype were lower in BC than the controls. Moreover this work revealed significantly higher frequencies of the T allele in BC patients than normal group.

This is in parallel with **Rizk et al.** [(15)], who reported a positive association between SIRT-1 (rs3758391) gene polymorphism and breast cancer risk. Also agrees with a study done by **Consiglio et al.,** [(16)] on systemic lupus erythematosus (SLE), who claimed that SLE patients with TT and CT genotypes had a more risk of developing lupus nephritis.

In contrast, **Rai et al.,** [(17)] find no significant association between SIRT1 expression and rs3758391 genotypes in a ethnic Indian group.

This study showed that the percentage of SIRT-1 T/T genotype were statistically significantly higher in BC patients with grade III than those with grade I + II.

This is agree with **Chen et al.,** [(18)] who revealed that high expression of SIRT1 was associated with poor outcome in a type of lung carcinoma patients, and added that, SIRT1 was related to histological grade of NSCLC patients, thus these researches support that SIRT-1 polymorphism can be considered as a promising marker of breast cancer**.**

Adding to this, the percentage of SIRT-1C/T and T/T genotypes were significantly higher in BC patients with tumor size T3 + T4 than those with tumor size T1 + T2. This is in accordance with **Lim,** [(19)] study**,** who postulated that increase expression of SIRT1 allows cancer cells to proliferate, which promote tumor progression.

In this study SIRT1, the percentage of SIRT-1 T/T genotype were higher in BC patients with LN infiltration N3 than those with LN infiltration N1+N2. So, from the previous results, SIRT1 was associated with poor histological grade of the tumor and the involvement of lymph node in BC patients.

This is in accordance with **Chung et al.,** [(20)] who revealed the SIRT1 role in breast tumor invasiveness and unfavorable clinical outcomes. Meanwhile, **Sung et al.,** [(8)] cleared that increased SIRT1 in tumor tissue of the breast were associated with a breast cancer of low grade.

SIRT1 serum levels in breast cancer were significantly higher as compared to the control group. Which were correlated positively with the size of the tumor, histological tumor grade and the involvement of lymph node in BC patients.

In a study done by **Abdelmawgoud and El Awady,** [(21)] they documented that expression levels of SIRT1 were higher in BC tissues in comparison to benign breast tumor and adjacent normal tissues. This is parallel with **Jin et al.,** [(22)] who recorded that SIRT1 is up-regulated in the human BC tissues. On the other hand, **Cao et al**. [(23)] reported a significant lower levels of SIRT1 expression in breast cancer tissues than in normal breast tissues.

Our data showed that SIRT-1 serum levels were significantly higher in BC patients with ER–ve and PR -ve than those with ER +ve and PR +ve. This agrees with Jin et al., who reported that SIRT1 is involved in the oncogenic pathway of estrogen/estrogen receptor (ER) in breast cancer [(22)].

Data obtained from this study, may postulate that SIRT1 levels and SIRT1 polymorphism may correlate breast cancer clinicopathological picture with disease progression and prognosis. Also data from this work clarify the role of SIRT1 genetic polymorphism as breast cancer risk factor.

V. CONCLUSION

Levels of SIRT1 is significantly increased in BC compared to control group and varied in study group according to tumor staging and lymph node infiltration. There was an association between SIRT1 gene polymorphism (rs3758391) and breast cancer risk, with the T allele stated as a risk factor. There was increment in SIRT1 serum levels in breast cancer patients, with more elevation in TT genotype.

VI. RECOMMENDATIONS

Summarizing the data obtained from this work, recommend the combined use of SIRT1 inhibitors and antiestrogen may give more efficient treatment protocol for breast cancer parallel with the classic approach for treatment.

Moreover, a better understanding of the molecular level of SIRT I and its impact on the signaling pathways, may provide opportunity for the development a new therapeutic approaches for BC cases.

STUDY LIMITATION

But owing to the debate, whether SIRT1 is a proapoptotic by reducing tumorigenesis or tumor promoting, more large-scale studies are needed in order to clear the role of the enzymatic duality of SIRT1 in breast carcinogenesis as well as its associated mechanisms.

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