Review Article

The expression of sirtuins in breast cancer and their prognostic and clinicopathological significance: a systematic review

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ABSTRACT

Objectives: Sirtuins (SIRTs) are a highly conserved family of enzymes that play an important role in cancer emergence and progression, including breast cancer. In this review, changes in the expression of different SIRTs in breast cancer and their association with metastasis and cancer grade were investigated.

Methods: This study was performed on 44 selected articles on breast cancer, which were extracted from PubMed, Scopus, and Web of Science. Among the selected articles, there were 31 case-control and 13 cohort studies with a total of 7326 and 4760 participants, respectively.

Results: In most studies, SIRT1, SIRT5, and SIRT7 expression levels were higher than the controls, while the expression levels of SIRT4 and SIRT6 were lower. Elevated levels of SIRT1 were associated with an increased risk of distant metastatic relapse (DMR), death, and recurrence, as well as reduced relapse-free survival (RFS). Additionally, there was a significant correlation between increased levels of SIRT1 and metastasis of lymph nodes and other tissues. Reduced levels of SIRT4 were associated with decreased overall survival (OS).

Conclusion: Our findings suggest that elevated levels of SIRT1, SIRT5, and SIRT7 may have potential value for use in the diagnosis of breast cancer. Increased levels of SIRT1 can be used as a prognostic marker..

Keywords: Sirtuins, Breast Cancer, SIRTs, clinicopathological, survival, prognostic

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Introduction

Sirtuins are a highly conserved family of enzymes with nicotinamide adenine dinucleotide (NAD)-dependent deacetylase or monoribosyltransferase activity (1). So far, seven isoforms of mammalian sirtuins (SIRT1–7) have been identified (2). Each sirtuin is determined by a conserved catalytic core domain of approximately 275 amino acids and an exclusive N-terminal and/or C-terminal sequences with variable length (3). Mammalian sirtuins are categorized according to their localization in different parts of the cell. The nucleus mainly contains SIRT1, SIRT6, and SIRT7, while the mitochondria encompass the majority of SIRT3, SIRT4, and SIRT5. SIRT2 is mainly located in the cytoplasm (4).

Due to the sirtuins' potential and ability to deacetylate both histone and various non-histone substrates, they modulate different main cellular functions, which may have a significant role in cancer. These enzymes are involved in the regulation of chromatin, cell differentiation and survival, aging, stress response, and metabolic homeostasis (5). Also, they have an important role in carcinogenesis and retention of the malignant phenotype through implication in cancer cell viability, apoptosis, metastasis, and tumorigenesis (4, 6). Despite a high degree of homology among members of the sirtuin family, they may have different activities in various types of cancer (7).

SIRT1 is the most studied member of the sirtuin family with two opposite functions not only in tumor promotion and suppression but also in tumor development (5, 7). It may play as an oncogenic factor or as a normal epigenetic modulator (7). SIRT2 may serve as a weak tumor inhibitor in carcinogenesis. Jing et al. showed that the inhibition of this sirtuin leads to vast anti-cancer activity in numerous cancer cell lines and mouse models of breast cancer (8). This anti-cancer effect is due to a decrease in the MYC level caused by the increased ubiquitination and degradation of MYC (7).

SIRT3 has a dual role in various kinds of cancer such as lung, gastric, and colon cancers (9). This sirtuin influences the tumorigenic process by regulating metabolism, depleting reactive oxygen species (ROS), and modulating the proliferation or apoptosis process (10). SIRT3 shows tumor suppressor activity by inhibiting proliferation (11). On the other hand, it can also demonstrate a tumor promoter function. However, its function in tumorigenesis is not yet clear (7).

SIRT4 presents tumor suppressor activities in breast, liver, and colorectal cancers (12). Its low expression in liver, gastric, lung, colon, and esophageal cancers is associated with poor clinicopathological grading (13). It may have an oncogenic role in tumors, but such a role needs to be investigated. An increase in the duplication of the SIRT5 gene has been detected in particular cancer types, including breast cancer, lung cancer, uterine cancer, cutaneous and uveal melanomas, and lymphoma (14). Although SIRT6 acts as a tumor suppressor by inhibiting genomic instability, regulating metabolic homeostasis, and retaining telomere integrity, there are accumulated data suggesting an oncogenic role for it in numerous types of cancer (15, 16). SIRT7 promotes tumorigenesis in different types of cancer, including breast cancer, ovarian cancer, hepatic cancer, gastric cancer, epithelial prostate carcinoma, and cholangiocarcinoma (17).

The prognostic and clinical value of abnormal expression of sirtuins in cancers is complex and requires further investigation. Therefore, in the present study, we aim to review the studies to reveal the changes in the expression of sirtuins in breast cancer and also show the association of sirtuins expression with metastasis and cancer grade.

Material & methods

Search strategy

A systematic review of the published relevant articles from 1997 to 2022 on the diagnostic value of sirtuins in human breast cancer and their association with metastasis, stage, and grade of cancer was performed. PICO was determined as follows and used for the data extraction:

• **Population:** Patients with breast cancer (human subjects; female; no age limitation)
- Breast cancer
- Cancer: neoplasm, neoplasia, carcinogenesis, adenoma, carcinoma, tumor

• **Intervention/Exposure:** Sirtuin expression
- Sirtuin, SIRT, class III histone deacetylase
- Expression: gene expression, protein expression, level, content, expression

• **Comparison:** Normal tissue (either from the same patient or control subjects)

• **Outcomes:**
- Main outcome: neoplasia (cancer transformation)
- 2nd outcome: metastasis, lymph node metastasis (LNM), distant metastatic relapse (DMR)
- 3rd outcome: grade, invasiveness, invasive characteristics, invasive
- 4th outcome: survival, overall survival (OS), disease-free survival (DFS); relapse-free survival (RFS)

• **Study design:** Case-control, cross-sectional, cohort

At first, the most important and appropriate electronic databases, including PubMed, Scopus, and Web of Science, were investigated based on the following search strategy to determine the role of sirtuins in breast cancer. The keywords used were: (1) cancer OR neoplasm OR neoplasia OR carcinogenesis; (2) breast; (3) #1 AND #2; (4) class-III AND "histone deacetylase"; (5) Sirt*; (6) #4 OR #5; and (7) #3 AND #6. Then, a list of titles and abstracts of all retrieved studies from the mentioned

databases was prepared and independently examined for the determination and selection of the relevant titles. The relevant studies were evaluated according to the blinding method and independently entered the research process.

Inclusion criteria and quality assessment of included studies

The main required criteria for inclusion of a study in our research was the evaluation of the expression level of sirtuins in breast cancer tissues compared with normal human tissues in that study. Clinical trials, studies without a control group, and in-vitro studies using cell lines and animal tissues were excluded from the research. Then, studies that satisfied the above-mentioned requirements were re-examined and duplicated articles were ruled out. To ensure that all included articles were in full compliance with inclusion and exclusion criteria, all articles were independently evaluated by three individuals, and disagreements were discussed and reviewed. The quality of each included study was evaluated by examining the article for compliance with inclusion and exclusion criteria, written consent form, and ethical approval. Articles with poor quality were removed.

Data extraction

The following data was extracted independently from each included study: title, name of journal, name of first author, publication year, country of study, type of study, study population, number of subjects, SIRTs expression level in tumor tissues in comparison with normal tissues, number of control subjects, range and mean of age, type of breast cancer, the measurement method of sirtuin, cancer grade, tumor size, lymph node status, metastasis, ER (Estrogen receptor) and PR (Progesterone receptor) status, the clinical stage of the disease, treatment

Table 1: Characteristics of 31 case-control studies.

References	Sirtuin	Case (N)	Control (N)	Comparison of SIRT in tumor vs. control
On-Yu Hong, et al. 2022	SIRT6	7	7	Increased
Shuai He, et al. 2022	SIRT5	120	120	Increased
Yanjing Jia, et al. 2021	SIRT1	85	85	Increased
Yanbo Yue, et al. 2020	SIRT1	80	80	Increased
Pengfei Shi, et al. 2019	SIRT2	296	296	decresead
Yiqun Yao, et al. 2019	SIRT1	20	20	Increased
Xiaoxia Jin, et al. 2018	SIRT1	100	100	Increased
Hamdy Swelim, et al. 2018	SIRT1, SIRT2, SIRT3	30	20	SIRT1 and SIRT3 = increased SIRT2 = decreased
Yifang Xu, et al. 2018	SIRT1	60	60	Increased
Hanan Abdelmawgoud, et al. 2017	SIRT1	60	24	Increased
Guoyu Huang, et al. 2017	SIRT4	94	86	Increased
Wenqi Shan, et al. 2017	SIRT1,2, 3,4, 5,6, 7	960	NA	Increased =SIRT7 Decreased=SIRT3
Mohammad Poorhosseini, et al. 2016	SIRT3	111	20	Not Significant
Sherine M. Rizk, et al. 2016	SIRT1	541	439	Increased
Wenwen Zhang, et al. 2016	SIRT1	149	1173	Decreased
Mehri IGCI, et al. 2016	SIRT1-7	64	64	Increased (SIRT2,3,5) Decreased (SIRT1 and SIRT4) Not significant (SIRT6 and SIRT7)
Wang L, et al. 2015	SIRT4	50	50	decreased
Ahmad Aljada, et al. 2015	SIRT7	128	16	Increased
Moran Choe, et al. 2015	SIRT6	150	8	Decreased
Qian Geng, et al. 2015	SIRT7	180	44	Increased
Shaozhong He, et al. 2014	SIRT3	308	NA	Not significant
Mohamed Mokhtar Desouki, et al. 2014	SIRT3	195	26	Decreased
Da Wang, et al. 2014	SIRT6	62	62	Decreased
Shou Jen Kou, et al. 2013	SIRT1	27	27	Increased
Kimberly R. Holloway, et al. 2013	SIRT1	90	10	Increased
Minqing Wu, et al. 2012	SIRT1	134	NA	Not significant
Hyun-Seok Kim, et al. 2011	SIRT2	36	45	Decreased
Ho Lee, et al. 2011	SIRT1	122	NA	NA
Gabriel Eades, et al. 2011	SIRT1	5	5	Increased
Ji-Youn Sung, et al. 2010	SIRT1	28	28	Increased
Hyun-Seok Kim, et al. 2010	SIRT3	36	38	Decreased
Ashraf N, et al. 2006	SIRT1 SIRT2 SIRT3 SIRT7	24	21	SIRT7= Increased No significant for SIRT1, SIRT2 and SIRT3 genes

response, inclusion and exclusion criteria, the existence of informed consent, hazard ratio, distant metastatic relapse (DMR), reduced relapse-free survival (RFS), overall survival (OS), disease-free survival (DFS), statistical analysis method, and outcomes achieved by evaluation of the relationship between SIRTs and metastasis, cancer grade, patient's lifetime, and prognosis of the disease. Then, the prepared table using the above-mentioned data was assessed for its included information by three other individuals.

Results

Search databases results

In the beginning, 2123 articles were found by a search of PubMed (471 articles), Scopus (664 articles), Embase (718 articles), and Web of Science (853 articles). After the exclusion of the duplicated and irrelevant studies, 54 articles remained. Then, the remaining 54 articles were precisely reviewed one more time according to the required inclusion and exclusion criteria, and 10 studies were omitted. Finally, 44 articles entered the analysis process (Fig. 1). To ensure that all included articles were in full compliance with inclusion and exclusion criteria, all articles were independently evaluated by three individuals, and disagreements were discussed and reviewed.

Characteristics of the eligible studies

Thirty-one case-control and 13 cohort studies were eligible for this review. They were published between 2006 and 2022. Among the 44 qualified articles, nine were conducted in the United States, three in the United Kingdom, 17 in China, seven in Korea, three in Egypt, one in Iran, one in Turkey, and one in the Netherlands. The number of patients in each case-control study ranged from 5 to 960 (a mean sample size of 134 patients) with a total of 5262 participants, while the number of patients in each cohort study ranged from 118 to 688 (a mean sample size of 344 patients) with a total of 4602 participants. Different studies have measured the levels of sirtuins in tumor tissues or serum by q-PCR, immunohistochemistry, bisulfite sequencing PCR, western blot, and microarray techniques.

The expression of sirtuins in breast cancer

Most case-control studies showed that the expression level of SIRT1 in patients with breast cancer was higher than in healthy individuals. From 19 case-control studies, 15 studies (18-32) reported an increase, three studies (33-35) reported a reduction, and one study (21)

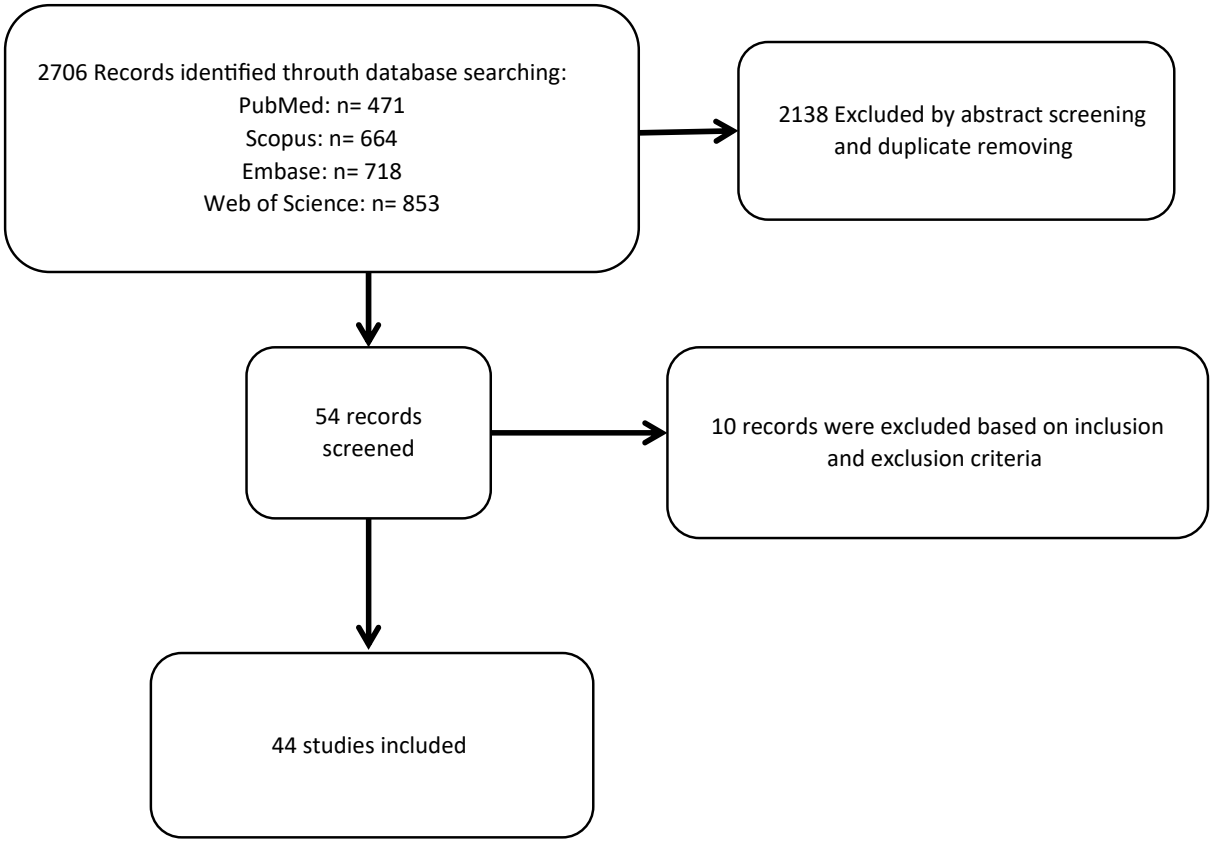

Figure 1: The process of entering studies in the systematic review.

Table 2: Characteristics of 13 cohort studies.

References	Sirtuin	Case (N)	Control (N)	Comparison of SIRT in tumor vs. control
Pengfei Shi, et al. 2019	SIRT2	296	296	decreased
Jie Tan, et al. 2018	SIRT1	268	215	Not Significant
Qingyu Shi, et al. 2016	SIRT4	409	241	Increased
Jeong-Ju Lee, et al. 2016	SIRT1, SIRT6	688	NA	Not Significant
Min-Sun Jin, et al. 2015	SIRT1	319	NA	Not Significant
Yul Ri Chung, et al. 2015	SIRT1	427	NA	Not Significant
Soo Young Chung, et al. 2015	SIRT1	344	NA	Not Significant
Hyojin Kim, et al. 2015	SIRT1	278	NA	Not Significant
Yu-Wen Cao, et al. 2014	SIRT1	150	150	Decreased
Remco S Derr, et al. 2014	SIRT1	460	NA	Increased
Liane M. McGlynn, 2014	SIRT1-7	117	25	Decreased (SIRT1 2, 3 6 & 7) Not significant= SIRT4
Mattaka Khongkow, et al. 2013	SIRT6	133	NA	Not Significant
Neill Patani, et l. 2011	SIRT1	127	31	Not Significant

reported no statistically significant difference between tumor and normal tissues for the SIRT1 expression level (Table 2).

Cohort studies (Table 2) also showed a difference between tumor tissues and normal controls for the SIRT1 expression. Among them, two studies by Derr RS et al. in 2014 (36) and Kim H et al. in 2015 (37) showed increased levels, two studies conducted by Cao YW et al. in 2014 (38) and Chung SY et al. in 2015 (39) showed decreased levels, and one study by Patani N et al. in 2011 (40) found no significant difference in SIRT1 expression levels in tumor samples compared to normal tissues. In addition, two other cohort studies, one by Lee JJ et al. in 2016 (41) and the other one by Tan J et al. in 2018 (42), reported increased expression of SIRT1 in 207 (30%) and 52 (20%) patients, respectively.

Six case-control studies investigated the expression level of SIRT2 in tumor samples compared to normal specimens and observed different results. Studies conducted by Swelim et al., Kim HS et al., McGlynn LM et al., and Shan et al. (35, 43-45) demonstrated decreased levels; while Igci et al.(34) showed increased levels of SIRT2 in breast tumors. A cohort study conducted in 2019 by Shi et al.(46) showed a reduction in SIRT2 levels in tumor tissues compared to healthy tissues. However, Ashraf et al.(47) reported no statistically significant difference in the levels of SIRT2 in tumor samples compared to healthy tissues.

Regarding SIRT3 expression levels in breast cancer tissues, four studies, including Desouki et al., Shan et al., McGlynn et al., and Kim et al. (45, 48-50), showed a significant reduction. Two studies, including D Swelim et al. and Igci et al. (34, 43), showed upregulation, and one study by Poorhosseini et al. (51) found no significant difference.

SIRT4 levels in tumor tissues were examined by five groups of researchers in two cohort and three case-control studies. Igci et al., Wang et al., Shi et al., and McGlynn et al. (34, 35, 52, 53) demonstrated a decrease, while another research group showed an increase in SIRT4 expression levels in breast cancer samples (54).

SIRT5 was studied by Igci et al. (34), McGlynn et al. (35), and He et al. (55). They showed that the SIRT5 expression level in tumor tissues is higher than the control. SIRT6 in case-control studies performed by Choe et al. (56), Wang et al. (57), and McGlynn et al. (35) showed a reduction, while Hong et al. (58) showed an increase in SIRT6 expression in tumor tissues in comparison to normal controls. However, Igci et al. (34) showed no significant difference. Among five studies conducted for the evaluation of the difference in SIRT7 levels between tumor tissues and normal specimens, four (21, 45, 59, 60) found an elevation, one demonstrated a reduction (35), and one revealed no difference in SIRT7 expression in breast cancer tissues compared to normal specimens (34).

Correlation between the expression of sirtuins and cancer prognosis

SIRT1

In a case-control study by Lee et al. (23), SIRT1 expression was significantly associated with DMR, RFS, and OS in univariate Cox regression analysis. Elevated levels of SIRT1 had a significant correlation with increased DMR (p=0.014) and RFS (p=0.027), and patients with upregulated levels of SIRT1 had a 3.8-fold (95% CI, 1.099-9.20) increased risk of death (OS, p=0.033) compared to patients with low expression of SIRT1. Likewise, in a case-control study, Wu et al. (61) reported a 2.963-fold (95% CI 1.38-6.245, p=0.005) increase in relapse risk ratio and a 3.687-fold (95% CI 1.345-9.567, p=0.011) increase in death risk ratio in breast cancer patients who had elevated levels of SIRT1 expression. In triple-negative breast cancer (TNBC) patients, the SIRT1 positive group showed 3.319 times

increased risk of DFS (95% CI 1.086-10.138, p=0.035) and 4.215 times increased risk of OS (95% CI 1.130-15.725, p=0.03) compared to the SIRT1 negative group. In non-TNBC patients, the SIRT1 positive group also had a 3.284-fold increase in DFS risk (95% CI 1.190-9.06, p=0.022) and a 5.135-fold increase in OS (95% CI 1.124-23.46, p=0.035) in comparison to the SIRT1 negative group. In addition, a cohort study by Derr et al. (36) showed a significant increase in tumor recurrence between patients with elevated levels of SIRT1 compared to patients with reduced levels of SIRT1. So, in patients with elevated levels of SIRT1, a remarkable decrease in RFS (1.32, 95% CI 1.03-1.70, p=0.03) was reported. Zhang et al. (33) showed that increased levels of SIRT1 are correlated with improved OS (88.38 months vs 101.03 months, p=0.025). A cohort study by Chung SY (39) in 2015 showed that increased SIRT1 plays an important role in the prognosis of TNBC patients (DFS: OR=1.766, 95% CI 1.098-2.832, p=0.020). Also, a study by RiChung Y (62) showed that an elevation in SIRT1 expression was associated with an increase in DFS (HR, 0.381; 95% CI 0.210-0.691; p=0.002). Cao et al. (38) revealed that reduced levels of SIRT1 were noticeably associated with poor prognosis of cancer (p=0.004, 95% CI 0.121-0.6, OS: expression (low vs. high) HR SIRT1=0.278, p=0.004, 95% CI 0.118-0.657, DFS: expression (low vs. high) HR=0.282).

On the other hand, in 2018, a study by Jie Tan et al. (42) demonstrated that increased SIRT1 expression was associated with a decrease in the relative OS (HR (95% CI): 1.855, 1.14-3.01). A cohort study by Jin MS in 2015 (63) also found that increased SIRT1 expression was associated with a decrease in patient survival. However, a cohort study by Patani et al. (40) showed no significant correlation between SIRT1 and DFS.

SIRT2

In 2019, a cohort study by Shi P et al. (46) indicated that the SIRT2 levels in tumor tissues were lower than in adjacent normal tissues. Also, the Kaplan-Meier diagram showed that the high expression level of SIRT2 in tumor tissues is associated with increased survival (p<0.05) in breast cancer patients. Patients with elevated levels of nuclear SIRT2 also had a significant decrease in DFS (5.7 years vs. 7.5 years, p=0.001) and 3.1-fold disease recurrence (p=0.002).

SIRT3

SIRT3 expression levels were examined by Desouki et al. (48). They reported that low expression of SIRT3 is significantly associated with a decrease in RFS (HR 0.53, 95% CI 0.47-0.61). A case-control study by He S et al. in 2014 (64) revealed that patients with increased expression of SIRT3 had a shorter DFS (33.8±4.5 vs. 45.5±6.9 months, p<0.001) and OS (15.8±7.2 vs. 23.9±5.7 months, p<0.001) than patients with diminished SIRT3.

SIRT4, SIRT5 and SIRT6

Overall survival time in patients negative for SIRT4 expression was noticeably shorter (70.35 months) than in patients with positive expression of SIRT4 (73.64 months) with a p-value of 0.0382. He et al. (55) reported that SIRT5 was a prognostic factor for patients with breast cancer. The study by Khongkow M et al. (65) showed that an increase in nuclear SIRT6 (the active form of SIRT6) was associated with poor survival (OS: p=0.018).

Correlation between the expression of sirtuins and clinic-pathological characteristics of cancer

Results of 8 studies (20, 22, 23, 29, 32, 39, 61, 62) showed that there is a significant correlation between elevated levels of SIRT1 and lymph node metastasis. However, the studies by Rizk et al. (24) and Shan W et al. (45) did not find a remarkable correlation between SIRT1 expression and lymph node metastasis. Cao et al. (38) and Kim H et al. (37) observed that decreased levels of SIRT1 were associated with lymph node metastasis, suggesting a tumor suppressor role for this sirtuin.

Data collected by Poorhosseini et al. (51) and Ashraf et al. (47) revealed that an increase in the expression level of SIRT3 in breast cancer samples is associated with lymph node metastasis and metastasis to other regions of the body, respectively. A study by He S et al. (64) also showed that SIRT3 expression was remarkably associated with lymph node metastasis. The results of two studies demonstrated that SIRT7 expression levels in the patient group with lymph node metastasis were higher than in the patient group without lymph node metastasis (Table 5).

Correlation between expression of sirtuins and cancer grade

SIRT1

In three case-control studies by Sherine M. Rizk et al. (24), Hanan Abdelmawgoud et al. (29), and Xiaoxia Jin et al. (66), it was revealed that SIRT1 was directly associated with tumor grade. At the same time, Mehri Igci et al. (34) showed that the expression levels of SIRT1 were correlated with grade 3 breast cancer (P=0.0002). A cohort study by Yu-Wen Cao (38) in 2014 demonstrated that high levels of SIRT1 were associated with tumor grade (high SIRT1, n=35 (72.9%) versus low SIRT1, n=13 (27.1%) in histological grade 3 breast cancer tissues (n=48), P=0.062). On the other hand, cohort studies by Jeong-Ju Lee et al. (41) and Ji-Youn Sunga et al. (20) showed that up-regulation of SIRT1

in breast tumor tissue was significantly associated with lower grade. However, Ho Lee MD et al. (23), Jie Tan et al. (42), N Ashraf et al. (47), and Neill Patani et al. (40) examined the expression status of SIRT1 in breast carcinomas and found no significant relationship between tumor grades and SIRT1.

SIRT2

The association between SIRT2 expression and breast cancer grade was investigated by different research groups. Mehri Igci et al. (34) showed that the expression level of SIRT2 was correlated with grade 3 breast tumor tissue ($P<0.0001$). However, no correlation between SIRT2 expression and the pathological grade of the breast tumor was reported by Pengfei Shi et al. (46) and N Ashraf et al. (47) ($p=0.921$).

SIRT3

Mehri Igci et al. (34) reported that the expression levels of SIRT3 were correlated with grade 3 breast cancer ($p=0.0421$). Similarly, Shaozhong He et al. (64) and Hamdy Swelim et al. (43) reported that SIRT3 expression was significantly correlated with tumor grade. In contrast, Hyun-Seok Kim et al. (50) and Liane M. McGlyn (49) showed decreased SIRT3 expression with increasing grade. However, Ashraf N et al. (47) and Mohamed Mokhtar Desouki MD et al. (48) reported no significant differences in SIRT3 expression with respect to tumor grade.

SIRT4

Guoyu Huang et al. (67) and Qingyu Shi et al. (68) did not find any significant associations between SIRT4 levels and pathological grade. Nevertheless, Mehri Igci et al. (34) showed that in breast cancer, SIRT4 plays a tumor suppressor role, and reduced SIRT4 expression was significantly correlated with tumor grade 3 ($P=0.0335$). Also, Liane M. McGlynn (35) demonstrated increased tumor grade with lower expression of nuclear SIRT4 ($p=0.039$).

SIRT5, SIRT6 and SIRT7

A study by Mehri Igci et al. (34) reported that SIRT5 expression was significantly correlated with tumor grade ($P=0.0135$). Liane M. McGlynn (35) showed that increased tumor grade was associated with low expression of cytoplasmic SIRT6 ($p=0.013$). The expression level of SIRT7 was significantly correlated with histological grade, as found by Qian Geng et al. (69) and Wenqi Shan et al. (45). They demonstrated that tumors with lower pathological grade tended to express less SIRT7. However, Ashraf N et al. (47) reported that SIRT7 expression was similar in different grades of tumor, and no significant differences in SIRT7 expression were reported in this study.

Discussion

In our investigation, we found that in most studies, SIRT1, SIRT5, and SIRT7 expression levels were increased, while SIRT4 and SIRT6 levels showed a decrease in tumors compared to normal tissues. The number of studies that showed an increase in the expression levels of SIRT2 and/or SIRT3 in tumors was equal to the number of studies with reduced levels of these sirtuins in normal controls, and there was no significant correlation between the expression levels of these two sirtuins and breast cancer.

Different studies have shown that elevated levels of SIRT1 play an important role in cancer progression (70). SIRT1 acts as an anti-apoptotic factor in tumorigenesis, deacetylating pro-apoptotic proteins and contributing to cell survival (7). It seems that high levels of SIRT1 are essential for estrogen/ERα-mediated oncogenic signaling. Various findings have been reported for other members of the sirtuin family. Regarding SIRT5, the overall findings support a tumor-promoting role for it in different types of cancer (71, 72). SIRT7 has an important role in lifespan extension and cell survival. Its knockdown leads to apoptosis of human cells (73). SIRT4 is considered a tumor suppressor in different types of cancers, including breast, liver, and colorectal cancers (12, 74). SIRT4 KO mice can spontaneously develop lung, liver, and breast cancers (75). Also, SIRT6 acts as a tumor inhibitor (7). This sirtuin interacts with a potential tumor suppressor called GCIP, which is downregulated in breast, colon, and prostate cancers (76).

Also, we found that in most studies, elevated levels of SIRT1 were correlated with poor prognosis, increased DMR, risk of recurrence, risk of death, and reduced RFS in breast cancer patients. In addition, a significant correlation was observed between SIRT1 and lymph node status, lymph node metastasis, and metastasis to other regions. It was reported in most studies that SIRT4 may play a tumor suppressor role in breast cancer, and its reduced level was correlated with decreased OS in patients. Therefore, according to the results of previous studies and our study, it can be concluded that SIRT1 may have the potential value of a biomarker to predict tumor metastasis in breast cancer.

In summary, according to the results of this study, it can be suggested that targeting SIRT1, SIRT5, and SIRT7 and their downstream pathways may pave a new road to finding more effective treatments for patients with breast cancer. Also, elevated levels of these three sirtuins may have potential value for the diagnosis of breast cancer, and increased levels of SIRT1 may be used as a prognostic marker of breast cancer. However, more studies are needed to elucidate the effects of sirtuins on the prognostic indexes, including RFS, DFS, OS,

metastasis, and cancer grade in patients with breast cancer.

Conflict of Interest

The authors declare no conflict of interest.

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