How to Cite:
Mohsin, M. A., & Zayed, K. S. (2022). Comparison FOXA1 expression in breast cancer patients and healthy persons. *International Journal of Health Sciences*, *6*(S7), 3556–3567.
https://doi.org/10.53730/ijhs.v6nS7.12573

Comparison FOXA1 expression in breast cancer patients and healthy persons

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***Abstract*---**Research for breast cancer (BC) biomarkers may lead to the discovery of novel therapeutic targets and predictive factors that will improve clinical outcome prediction. Forkhead box protein A1 (FOXA1) is pioneer factor serves both as a growth stimulant and a repressor and the significance role of this protein as a prognostic and therapeutic biomarkers still controversial, so the aim of this study was identify the precise role of FOXA1 protein expression in prediction of BC patients outcome, recurrence and treatment of BC by immunohistochemical (IHC) staning method. The current research was done during the period September 2021 and May 2022 at the University of Kufa's, Faculty of Medicine, Middle Euphrates Unit for Cancer Research. In this study, Seventy three tissues samples embedded in wax block taken from BC patients with (52.71+11.55) years who had surgery between 2014-2020 and thirty seven of normal (non tumoral) breast tissues samples with (54.17$\pm$10.84) years as a control group. These samples collected from archieves of the two private laboratories and re-evaluted by two pathologist. Positive nuclear IHC expression of FOXA1 is considerably reduced in 43 BC cases (58.9%) compared to 38 control individual (100%). Negative nuclear IHC expression of FOXA1 was considerably reduced in BC patients, 30 cases (41.1%) compared to 0 control persons (0.0%), Odd ratio 1.66, 95% CI (1.37-1.98), P=0.0001. Moreover, FOXA1 positivity was elevated considerably in patients with invasive ductal carcinoma (IDC), (P=0.002), grade I and II (P=0.002). This study concluded, negative FOXA1 expression increased in patients than healthy persons.

***Keywords*---**FOXA1, IHC, Breast Cancer

Introduction

The most prevalent kind of cancer in women worldwide is BC. It accounts for 25% of all malignancies, and in the past 25 years, the number of cases has more than doubled.. (Ghoncheh *et al.*, 2016). Women's tumors are most commonly caused by lung cancer, followed by BC. It accounts for 14% of all cancer-related deaths, Each year, almost 2.1 million women are diagnosed with BC, and 626,679 deaths (Bray *et al.*, 2018; Zafar *et al.*, 2019). The BC incidence rate in Iraq progressively from 8.56% of all newly diagnosed cancers in 2008 to 19.55% in 2020 as the most prevalent cancer in Iraq (ICR, 2020). Estrogen receptor (ER) was expressed in most of BC. Two-thirds of all BCs are luminal subtypes, and ER activity is essential for their growth (Carroll *et al.*, 2005). Because estrogen signaling is necessary for the progression of ER-positive BC, ER inhibitors can be used to treat the condition (Ali and Coombes, 2002). Current BC care includes a variety of clinicopathological characteristics, including tumor size, histological subtype and grade, lymph node status, and the expression of ER, progesterone receptor (PR), and human epidermal growth factor (HER-2). However, these characteristics only have a limited ability to accurately predict a person's survival (Habashy *et al.*, 2008). It is very important to find new biomarkers that can predict how BC will progress so that clinical management can be improved and new therapeutic targets can be found. ER activity can be changed by a number of proteins, such as coactivators and corepressors, as well as the recently discovered "pioneer" factor, FOXA1 (Carroll *et al.*, 2005; Laganière *et al.*, 2005). FOXA1 was one of three proteins in the FOXA family. It controls tissue-specific transcriptional programs and was involved in cell growth, proliferation, apoptosis, differentiation, and development in a variety of organs, including the pancreas, prostate, and breast (Zaret *et al.*, 2011; Bernardo and Keri, 2012). FOXA1 has been demonstrated to play both a growth stimulator and a repressor in BC, In the early stages, it promotes tumor growth, but later on, it suppresses tumor growth (Hu *et al.*, 2014). Therefore, we carried out this research to examine the relationship between FOXA1 expression with the age, grades, and some of histological types of BC in Iraqi women.

Materials and Methods

This research was carried out between September 2021 and May 2022 at the University of Kufa's Faculty of Medicine, Middle Euphrates Unit for Cancer Research.

Collection of Samples

Patients Group

This study is carried out on seventy three cases of BC their Paraffin blocks gathered from surgical BC patients between 2018 and 2022. The archives of two private laboratories were used to collect the data retroactively. Each pathologic specimen was histologically reevaluated by two pathologists, Electronic medical records of these laboratories are used to obtained the clinicopathological characteristics of patients which includes age, histological subtypes and grade. However, these data were used to determine FOXA1 protein expression in BC

patients and normal tissue subject as controls and investigation the correlation between FOXA1 and these clinicopathological features.

Control group

Thirty eight blocks of normal non-tumoral breast tissue has been gathered randomly from archives of three private laboratories during the collection of BC tissue blocks, and also, re-evaluated by two pathologist to ensure their normality.

IHC Procedure

One hundred eleven blocks of Paraffin were prepared for FOXA1 by Labeled Streptavidin Biotin (LSAB) method, Five μm thickness sections have been cut from paraffin-embedded blocks and set on positively charged slides.

Control of IHC

In IHC study , two controls were used:

A: Positive control: Paraffin blocks of BC were prepared and dyed as positive control for FOXA1 in every run.

B: Negative control: Untreated slides with primary antibody were regarded as negative controls for each slides set.

Results of Staining

Only tumour cells that have nuclear positivity are included for assessment. Evaluation takes into account both staining ratio (the percentage of stained cells) and intensity. The staining ratio is recorded as 0 (0%), 1 (>0% to 25%), 2 (>25% to 50%), 3 (>50% to 75%), and 4 (>75%), whereas the intensity was marked as (negative), 1 (weakly positive), 2 (moderately positive), or 3 (strongly positive). The overall protein expression score = staining intensity score × staining extent score, which was graded and divided into five scores according to this equation, 0(0%), 1 (1–25%), 2 (26–50%), 3 (51–75%) and 4 (76–100%). (Yuan *et al.*,2020).

Statistical Analysis

The data were analyzed using SPSS version 21. Numeric variables were reported as mean ± SD and nominal variables as number and percent when variables were regularly distributed, the Student t-test is used to compare means between two groups, whereas the Mann Whitney U test was used to do so, when the distribution of the variables was not normal. When the chi-square test cannot be used because it is invalid, the corrected chi-square test was utilized. Odd ratios with a 95% confidence interval (CI) and were used to estimate risk.

Results

Nuclear expression of FOXA1 protein in BC patients and control

Nuclear positive FOXA1 expression was reduced considerably in patients group 43 persons (58.9%) comparative to the control group 38 persons (100%) while the negative FOXA1 expression was reduced considerably in patients group 30 persons (41.1%) comparative to control group 0 persons (0.0%) (P=0.0001). Odd ratio for this protein was 1.66 95% CI (1.37-1.98), (Table 1), (Figures 1 to 4).

Table 1: FOXA1 nuclear expression in two groups of the study.

Nuclear IHC of FOXA1 expression	Control Group		Patients Group		Odd ratio (CI^+ %95)
	No.	%	No.	%	
Positive expression	38	100.00	43	58.9	1.66 (1.37-1.98)
Negative expression	0	0.0	30	41.1	
Total	38	100.00	73	100.00	

P=0.0001, CI^+= Confidence interval, Pearson Chi-Square Test

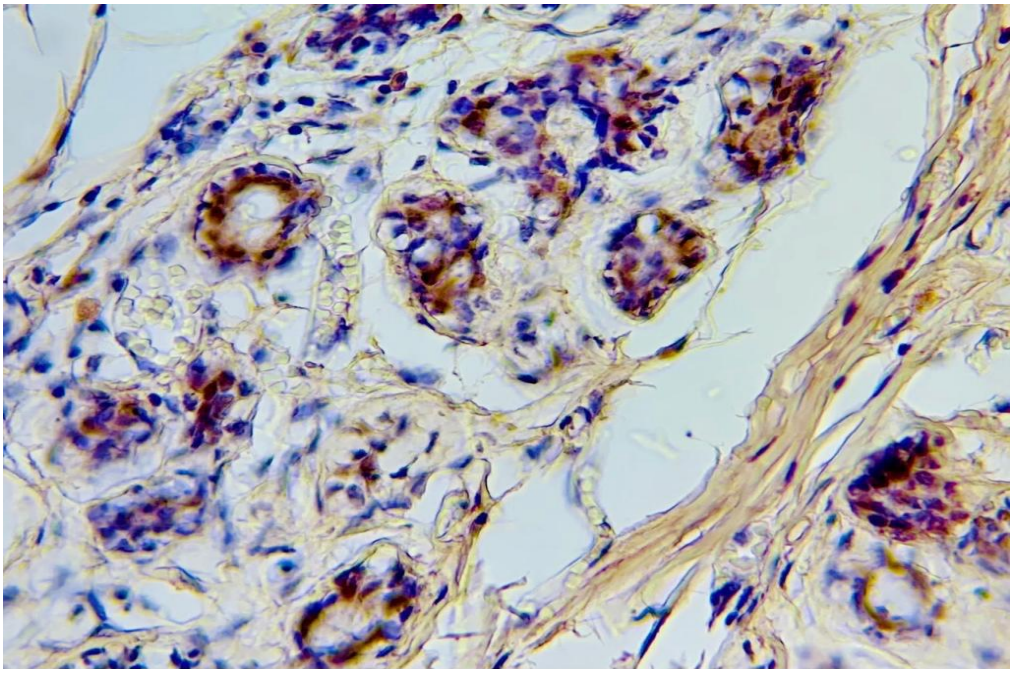

Figure (1): Normal tissue, positive nuclear stain for FOXA1 by IHC technique 400X.

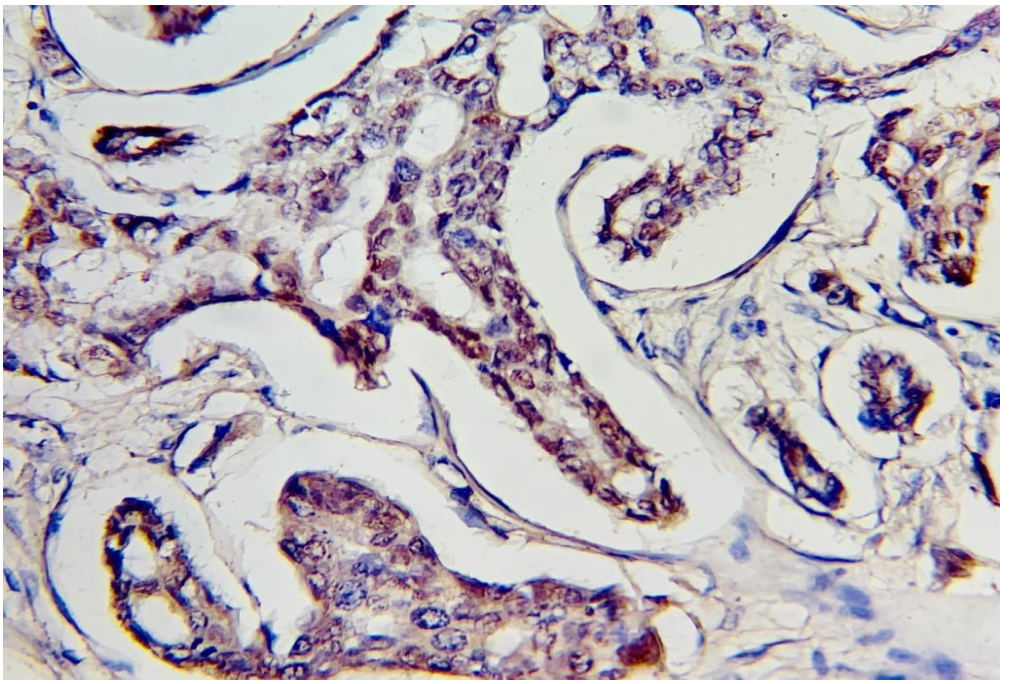

Figure (2): Moderately differentiated IDC, positive nuclear stain for FOXA1 by IHC technique 400X.

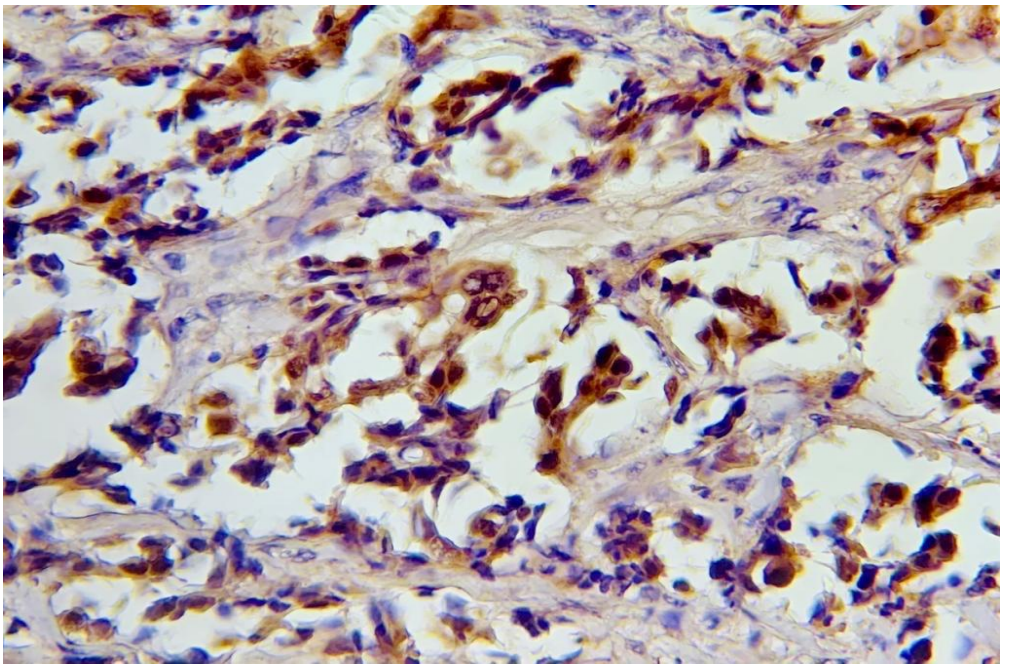

Figure (3): Poorly differentiated IDC with focus of in situ carcinoma, diffuse positive nuclear stain for FOXA1 by IHC technique 400X.

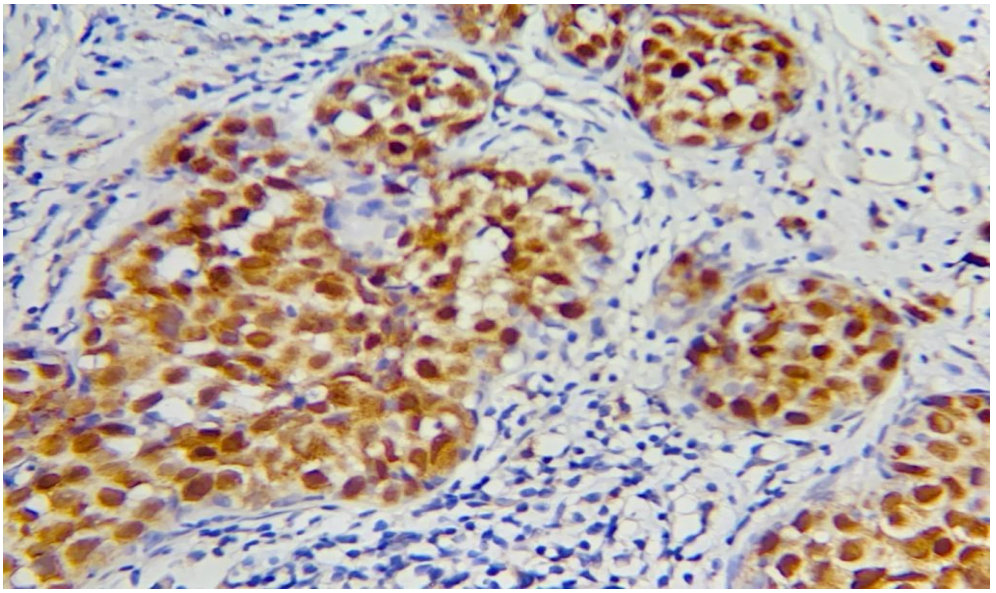

Figure (4): Tru cut biopsy, Moderately differentiated IDC. diffuse positive nuclear stain for FOXA1 by IHC technique 400X.

The clinicopathological characteristics of patients and control groups

Seventy-three Iraqi BC patients were enrolled in this study who mean age mean was (52.71+11.55) years in addition to thirty-eight individuals as a control group who mean age was (54.17±10.84) years. Statistically, there was no significant difference (p=0.737) between two groups which reflected a coordinated parallel match in mean age between two groups and fulfilling the requirement to conduct this study as seen in (table 2). On the other hand, the percentage of patients with age more than 50 years was 56.2% and the patient's percentage with equal or less than 50 years was (43.8%) as showed in (table 3). Furthermore, the patients group was Histologically separated into two subgroups; IDC and invasive lobular carcinoma (ILC). Majority of cases 58 (79.5%) were IDC subtype while ILC subtype was 15 cases (20.5%). According to BC grades, the distribution prevalence of cases in this study were 13 (17.8%), 38(52.1%) and 22(30.1%) as grade I, grade II and grade III of BC consequently.

Table 2 The percentage of patients and control group according to the age

Variable	Group (N)	Mean±SD	P.value
Age	Control (38)	54.17±10.84	0.737
	Patients (73)	52.71±11.55	

Independent T- test

Table 3: The clinicopathological characteristics of BC patients

Clinicopathological features	No.	%
Age		
≤ 50	32	43.8
>50	41	56.2
Histological subtypes:		
IDC	58	79.5
ILC	15	20.5

Association some clinicopathological features with FOXA1 protein expression:

BC patient's age and FOXA1 protein expression:

There was no significant difference in FOXA1 protein expression in BC patients age equal or less than 50 years old comparative to 50 years old (P=0.581) as shown in (Table 4).

Table 4: BC patient's age and FOXA1 protein expression.

Age	Total Count	FOXA1 Protein		Total
		Positive expression	Negative expression	
≥50 years	**No.**	20	18	38
	%	62.5%	31.0%	%100
<50 years	**No.**	23	12	35
	%	56.1%	80.0%	%100
Total	**No.**	43	30	73
	%	58.9%	41.1%	100%

P=0.581, Pearson Chi-Square Test

Some histological types of BC & FOXA1 protein expression

Nuclear positive FOXA1 expression was elevated considerably in patients with IDC 40 patients (69.0%) comparative to ILC patients 3 individuals (20.0%%) (P=0.002), (Table 5).

Table (5): BC histological types and FOXA1 expression.

Histological Type of BC	Total Count	FOXA1 Protein		Total
		Positive expression	Negative expression	
IDC	No.	40	18	58
	%	69.0%	31.0%	100%
ILC	No.	3	12	15
	%	20.0%	80.0%	100%
Total	No.	43	30	73
	%	58.9%	41.1%	100%

P=0.002, Pearson Chi-Square Test

Discussion

FOXA1 expression in BC patient and control

Positive FOXA1 expression decreased significantly in BC patients than control with normal breast tissue (Table 3-1). The findings of this study indicate that the majority of BC cases was positive FOXA1 expression 58.9% while negative FOXA1 expression 41.1%. Other studies showed, positive nuclear FOXA1 expression was detected in 32 cases (45.7%) while 38 cases (54.3%) were negative for FOXA1 expression (Abelzaher *et al.*, 2022). Besides, positive FOXA1 expression was detected in 84.6% of cases while negative FOXA1 expression was 15.4% of cases (Rangel *et al.*, 2018). Other finding claimed, positive FOXA1 expression was 74% in BC caces (Badve *et al.*, 2007). Furthermore Habshy *et al.* (2008), Mehta *et al.* (2012), Guiu *et al.* (2018) revealed that positive FOXA1 expression were (55%), (85%), and (55%) respectively. As a result of overexpression, mutation, or amplification, the expression and function of FOXA1 are not working as they should. This creates difficulties for endocrine and HER2-targeted treatments which regarded worse for patients (Razavi *et al.*, 2018, Fu *et al.*, 2019). Nuclear receptor crosstalk can change the way that FOXA1 chromatin binds, which can also lead to therapeutic resistance and the activation of compensatory pathways. (Karmakar *et al.*, 2013, Hoffman *et al.*, 2018, Tonsing-Carter *et al.*, 2019). Nakshatri-Badve (2009) said that a decreased in FOXA1 expression during the progression of cancer was caused by a rise in the activity of the polycomb complex, which helps silence Hox genes by changing the structure of chromatin during embryonic development. It has been demonstrated that CDH1 is an essential component in the process of epithelial mesenchymal transition (EMT). FOXA1 increases the protein expression of CDH1 by stopping the expression of

Slug in BC. This showed that EMT-progression was controlled by the balance of the FOXA1-slug axis (Anzai *et al.*, 2017). The presence of FOXA1 has also been associated to a better prognosis in BC patients who have been treated with Tamoxifen (Matt *et al.,* 2015). IL6 was induced when FOXA1 expression was decreased, which results in BC cells with tamoxifen resistance having characteristics similar to cancer stem cells (Yamaguchi *et al.*, 2017). According to Horimoto (2015), Patients with high FOXA1 expression were more likely to have late recurrences of BC than those with low expression. Cross-talk between FOXA1 and ER can increase differentiation-associated gene expression, but not proliferation-associated gene expression, resulting in breast carcinomas with ER positivity that are well-differentiated with good prognosis (Hu *et al.*, 2014). FOXA1 high expression, which is a tumor suppressor, could stop the spread of cancer by changing the expression of p27 (a BRCA1-related cell cycle inhibitor) and increasing the expression of CDH1 (Habashy *et al.*, 2008). Arruabarrena-Aristorena *et al.* (2020) revealed FOXA1 hotspot mutations, which are well-known contributors to endocrine therapy resistance, were more prevalent in metastatic ER-positive patients than in initial ER-positive BC and were incompatible with *ESR1* (estrogen receptor1) mutations. The SY242CS mutation in particular displayed neomorphic characteristics, including the capacity to access other chromatin areas and activate an alternate cistrome and transcriptome. The team's structural models showed that SY242CS causes a change in conformation that allows it to bind to a non-canonical DNA motif in a stable way. SY242CS mutation upregulated genes that are involved in cell growth and tumor formation. The mutation also gave FOXA1 the ability to change the way chromatin is accessible and activate a unique cistrome, which in turn caused the expression of a different transcriptome .Other SY242CS-specific gene effect includes an increase in lipid synthesis, which may serve as a source of energy to support the mutant's elevated proliferation rate.

Association of some clinicopathological features with FOXA1 expression

In this study , FOXA1 positive expression was significantly correlated with IDC , while most cases of negative FOXA1 was ILC (Table 3-5). There were correspondences between the attitudes expressed by this study and those described by (Habashy *et al.*, 2008; Mehta *et al.*, 2012; Cheng *et al.*, 2020). On other hand, The level of FOXA1 protein expression was lower in IDC than in ILC, which had the highest level of all the histologic types (Cheng *et al.*, 2020). This findings are contrary to that of (Wolf *et al.*, 2007; Thorat *et al.*, 2008; Albergaria *et al.*, 2009) who found that There was no correlation between FOXA1 expression and any of the histological subtypes of BC. This study concluded, negative FOXA1 expression increased in patients than healthy persons.

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