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Association Between Irisin Gene rs3480 Polymorphism and Breast Cancer

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Abstract:

The prevalence of breast cancer is rising worldwide. Irisin is a novel myokine that is proteolytically processed from the product of the FNDC5 gene. The study aims to assess the possible association of FNDC5/irisin gene polymorphism (rs3480) with the development of breast cancer. This study included 50 breast cancer patients and 50 healthy females matched for age as a control group. All subjects were submitted to full history taking, general clinical examination, pathological and radiological examination for grading and staging of the tumor, and laboratory investigations including CBC, Liver function tests (ALT, AST, serum albumin, serum bilirubin), lipid profile (TC, TG, LDL, HDL), Serum levels of CEA and CA 15–3 and genotyping of rs3480 (A/G) gene polymorphisms. There was a significant statistical difference between the two groups regarding the genotype frequency of FNDC5 (Irisin precursor) rs3480 (A/G). Regarding rs3480 (A/G), there was a high frequency of AA genotype and A allele among the control group. In contrast, GG genotype and G allele had the highest frequency among the breast cancer patient group. Multivariate analysis reveals that elevated cholesterol OR (1.312) (1.008-1.709), TG OR (1.074) (1.028-1.123), and GG genotype OR (5.052) (1.182-53.646) are significant risk factors for breast cancer. Conclusion: Our results indicate that GG genotype and G allele of rs3480 (A/G) polymorphism could be a risk factor for breast cancer.

Keywords: breast cancer, Irisin, gene polymorphism, allele, FNDC5.

1. Introduction

Breast cancer (BC) is the most frequently diagnosed cancer and a major health issue in women. WHO recorded over 2.3 million new cases every year, representing (11.7%) cancer in both sexes. It is also the leading cause of cancer death in women accounting for (6.9%) of all cancer-related mortality (1).

In Egypt, BC incidence is among the highest in the Middle East. It is the second most common cancer in Egypt, accounting for (16.4%) of total cancer cases. It is the most prevalent cancer among Egyptian women as it constitutes (32.4%) of female cancers. It is also the second leading cause of cancer death accounting for (10.3%) of all cancer-related mortality (2).

Irisin, a recently discovered myokine, was named after the ancient Greek messenger goddess Iris, whose role was to deliver messages to the gods living on Mount Olympus. The protein released by the exercising muscle was thought to play a similar role in delivering messages to tissues in the body and bringing them the beneficial effects of exercise, therefore justifying the naming (3).

The role of FNDC5/irisin in the occurrence and prevention of cancer has received extensive attention. Irisin has a wide application prospect for cancer treatment (3).

Aim of work

The study aims to assess the possible association of FNDC5/irisin gene polymorphism (rs3480) with the development of BC.

2.Subject and methods

Subjects:

This is a case-control study, which was carried out in Clinical Pathology Department, Faculty of Medicine, Mansoura University. BC patients' samples were selected from the Oncology Center, Mansoura University. The study included two study groups: Group I: which included 50 BC patients. Group II: included 50 age-matched, apparently healthy female subjects as a control group. All subjects were submitted to full history taking, general clinical examination, and laboratory investigations including CBC, Liver function tests (ALT, AST, serum albumin, serum bilirubin), lipid profile (TC, TG, LDL, HDL), Serum levels of CEA and CA 15–3 and genotyping of rs3480 (A/G) gene polymorphisms. Pathological and radiological examination for grading and staging of the tumor for the BC patient group.

Sample collection and assay procedure:

Prior to the collection of samples, written consent forms (approved by the Committee of Human Rights in Research at Mansoura University) were obtained from all studied subjects. Ethical approval was obtained from the Institutional Review Board (IRB) at the Faculty of Medicine, Mansoura University (Code Number: MS:23.12.2662). Written informed consent was obtained from each participant in the study.

8 ml of venous blood was collected from each subject under complete aseptic conditions, and the blood sample was divided as follows: 2 ml of blood was delivered into an EDTA tube for CBC,4 ml of blood was delivered into a plain tube and left until clotting then the tube was centrifuged for 10 minutes at a speed of 3000 r.p.m. The separated serum was used for routine laboratory investigations (serum creatinine, ALT, AST, serum albumin, serum bilirubin, lipid profile, serum level of CEA & CA 15–3), and 2 ml of blood was delivered into an EDTA tube properly labeled and stored at -20°C for further molecular analysis.

DNA extraction was done using GeneJET Whole Blood Genomic DNA Purification Mini Kit (Thermo Scientific, USA, Cat. no #K0781).

Genotyping of FNDC5/Irisin gene (rs3480) variant was performed by real-time PCR using TaqMan SNP Genotyping on StepOne Real-Time PCR System (Applied Biosystems, USA). F-primer 5'AGCTCTTGTAGACCGGAAGGAA3',R-primer 5'TGGTCCCCAAGCCAGAGA3'
FAM (G allele)5'CCATCACCCAATGAC3'Hex (A allele) 5'AGCCATCACCTAATGAC3'

The genotyping reaction mix was prepared by mixing TaqMan master mix 10 µl, Forward primer 0.5 µl, Reverse primer0.5µl, FAM probe 0.5 µl, Hex probe 0.5 µl, DNA template 5 µl, and Nuclease-free water 3 µl.

Reaction conditions were carried out with the following cycling stages: Stage I: at 95˚C for 10 minutes (initial denaturation). Stage II: includes 40 cycles of denaturation at 95˚C for 15 seconds and annealing/extension at 60˚C for 60 seconds. Stage III: 60˚C for 30 seconds (final extension).

Statistical Analysis:

Data was entered and analyzed using IBM-SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Qualitative data was expressed as N and percentage (%), was initially tested for normality using Kolmogorov-Smirnov test and was expressed as mean ± standard deviation (SD) if normally distributed or median and range if not. Data comparison: Qualitative data: Chi-Square test or Fisher's exact test was used. Quantitative data for two groups: Independent-Samples t-Test for parametric data or its non-parametric equivalent; Mann-Whitney U test was used. Quantitative data for more than two groups: ANOVA for parametric data or its non-parametric equivalent; Kruskal-Wallis test was used. The OR and 95% confidence interval (95% CI) were used to assess the association between different genotypes and BC and its clinical symptoms. A p-value is considered significant if <0.05 at confidence interval 95%.

3. Results

This study included 50 breast cancer patients and 50 healthy females matched for age as a control group. There was a statistically significant difference between the two studied groups regarding BMI is significantly increased in the BC group compared to the control group. COC administration is considerably more frequent in the BC group compared to the control group. While there was no significant difference regarding age and marital status (Table 1, figure 1).

As regarding Clinical characteristics of the studied BC patients, the mean onset age among the studied patients is (49.3 ± 11.80). Most patients (92.0%) have unilateral BC. IDC is the most common tumor type among patients (80.0%). Both ER and PR are positive in 66.0% of patients. HER2 is positive for 52.0% of patients. As regards TNM staging, T2, NI, and M0 are the most common stages among patients (62.0%, 42.0%, and 60.0%, respectively). 38.0% of patients are stage II, 34.0% are stage IV, and 18.0% of them are stage III (table 2).

As regarding (AST, ALT, CEA, CA15-3, cholesterol, TG, LDL, HDL Hemoglobin, PLT, albumin, WBCS, Creatinine, Bilirubin). Hemoglobin and albumin are significantly decreased in the BC group compared to control group. There is significant elevation of AST, CEA, CA15-3, cholesterol, TG and LDL in the BC group compared to control group (table 3, figure 2,3,4).

As regards FNDC5 rs3480 (A/G) genotype distribution between the two studied groups; it showed a significant statistical difference, with increased frequency of the GG and AG genotypes and G allele in BC patient group and increased AA genotype and A allele frequency in the control group (P <0.001); (Table 4).

Regression analysis was conducted for the prediction of BC from control, using BMI, COC, some laboratory parameters, and FNDC5 gene (rs3480) polymorphism as covariates. Univariate analysis revealed that elevated BMI (OR=1.079; 95%CI=1.019-1.142, p=0.009), COC (OR=3.857;95%CI=1.278-11.638, p=0.017), elevated AST (OR=1.068; 95%CI=1.008-1.132, p=0.025), elevated CEA (OR=0.002; 95%CI=1.171-1.951, p=0.002), elevated CA15-3 (OR=1.160; 95%CI=1.056-1.263, p=0.001), elevated cholesterol (OR=1.316; 95%CI=1.019-

1.612, p≤0.001), elevated TG (OR=1.070; 95%CI=1.044-1.097, p≤0.001), elevated LDL (OR=1.308; 95%CI=1.069-1.600, p=0.009), and GG genotype (OR=6.459; 95%CI=1.275-32.692, p=0.024), were significant risk factors for BC. Meanwhile, elevated Hb (OR=0.410; 95%CI=0.256-0.656, p≤0.001) and albumin (OR=0.051; 95%CI=0.010-0.078, p≤0.001) were significant protective factors for BC. Multivariate analysis revealed that elevated cholesterol, TG, and GG genotypes were significant risk factors for BC (p=0.010, 0.001, and 0.049, respectively) (table 5).

Table 1: Demographic and clinical characteristics of the studied groups.

Parameter		**Control group (n=50)**	**BC group (n=50)**	**P value**
Age*	Mean ± SD	52.2 ± 14.8	53.3 ± 11.6	0.670
BMI*	Mean ± SD	31.1 ± 6.98	35.1 ± 7.60	0.007
BMI group**	18.5-24.9	15 (30.0%)	4 (8.0%)	0.019
	25.0-29.9	9 (18.0%)	11 (22.0%)	
	≥30.0	26 (52.0%)	35 (70.0%)	
Family history**	Negative	50 (82.0%)	38 (76.0%)	0.461
	Positive	0 (0%)	12 (24.0%)	
Marital status**	Single	11 (22.0%)	4 (8.0%)	0.091
	Married	39 (78.0%)	46 (92.0%)	
COC**	Negative	45 (90.0%)	35 (70.0%)	0.012
	Positive	5 (10.0%)	15 (30.0%)	

Independent sample T test*, Chi-Square test (Fisher's Exact test) **. COC: combined oral contraceptive. significant (P value < 0.05)

Table (2): Clinical characteristics of the studied BC patients.

Parameter		**BC patients**
Onset age of BC	Mean ± SD	49.3 ± 11.80
Tumor site	Unilateral	46 (92.0%)
	Bilateral	4 (8.0%)
Tumor size	Median (min-max)	2.3 (1.0-12.4)
Tumor type	Paget	1 (2.0%)
	DCIS	6 (12.0%)
	IDC	40 (80.0%)
	ILC	3 (6.0%)
ER	Positive	33 (66.0%)
PR	Positive	33 (66.0%)
HER2	Positive	26 (52.0%)
KI67 (%)	Median (min-max)	30.0 (5.0-80.0)
T staging	Tis	5 (10.0%)
	T1	10 (20.0%)

	T2	31 (62.0%)
	T3	3 (6.0%)
	T4	1 (2.0%)
N staging	N0	15 (30.0%)
	N1	21 (42.0%)
	N2	10 (20.0%)
	N3	4 (8.0%)
M staging	M0	30 (60.0%)
	M1	20 (40.0%)
Staging	Stage 0	3 (6.0%)
	Stage I	2 (4.0%)
	Stage II	19 (38.0%)
	Stage III	9 (18.0%)
	Stage IV	17 (34.0%)

DCIS: Ductal carcinoma in situ. IDC: Invasive ductal carcinoma. ILC: Infiltrating lobular carcinoma. ER: estrogen receptors. PR: Progesterone receptors. HER2: Human epidermal growth factor receptor 2.

Table (3): Comparison of laboratory results between the studied groups.

Parameter		**Control group (n=50)**	**BC group (n=50)**	**P value**
Hb g/dl	Median (Min-Max)	12.6 (10.5-14.0)	11.7 (6.5-13.7)	≤0.001
WBCS ×109 /L	Median (Min-Max)	7.3 (3.8-12.4)	7.1 (3.4-18.7)	0.978
PLT ×109 /L	Median (Min-Max)	285.9 (156.3-398.1)	270.3 (34.1-372.0)	0.065
AST U/L	Median (Min-Max)	19.2 (14-45)	22.7 (15-247.5)	0.017
ALT U/L	Median (Min-Max)	20.5 (15-32)	22.5 (15.0-151.2)	0.452
Albumin g/dl	Median (Min-Max)	4.0 (3.5-5.0)	3.5 (2.7-4.0)	≤0.001
Bilirubin mg/dl	Median (Min-Max)	0.7 (0.4-1.0)	0.8 (0.4-2.4)	0.956
Creatinine mg/dl	Median (Min-Max)	0.9 (0.6-1.2)	1.0 (0.6-1.8)	0.899
CEA ng/mL	Median (Min-Max)	2.0 (0.8-5.3)	4.1 (0.9-161.9)	≤0.001
CA15-3 U/mL	Median (Min-Max)	6.7 (1.4-20.6)	17.6 (1.8-800.0)	≤0.001
Cholesterol mg/dl	Median (Min-Max)	146.0 (118-169)	242.5 (176-346)	≤0.001
TG mg/dl	Median (Min-Max)	66.5 (50-148)	136.0 (76-190)	≤0.001
HDL mg/dl*	Mean ± SD	50.7 ±9.73	48.5 ± 11.23	0.289
LDL mg/dl	Median (Min-Max)	76.1 (44.4-111.8)	156.7 (101.8-283.8)	≤0.001

independent sample T test*, Mann-whitney tests. CEA: Carcinoembryonic antigen. CA15-3: Cancer antigen 15-3.

Table (4): Distribution of FNDC5/Irisin gene (rs3480) genotype variants and alleles in BC patients versus controls.

		Control group (n=50)	BC group (n=50)	Relative risk of BC			
				OR	95%CI		P
AA	Count (%)	33 (66.0%)	23 (46.0%)	1	-	-	R
AG	Count (%)	15 (30.0%)	18 (36.0%)	1.721	0.723	4.100	0.219
GG	Count (%)	2 (4.0%)	9 (18.0%)	6.459	1.275	32.692	0.024
AG+GG	Count (%)	17 (34.0%)	27 (54.0%)	2.278	1.016	5.108	0.045
A	Count (%)	81 (81.0%)	64 (64.0%)	2.398	1.257	4.571	0.007
G	Count (%)	19 (19.0%)	36 (36.0%)				

OR: odds ratio.

Table (5): Logistic regression analysis for prediction of BC from control.

		Univariate analysis				Multivariate analysis			
		p	OR	95% CI		P	OR	95% CI	
BMI		0.009	1.079	1.019	1.142	0.681	1.028	0.903	1.170
COC		0.017	3.857	1.278	11.638	0.527	1.431	0.923	5.845
Hb		≤0.001	0.410	0.256	0.656	0.439	0.681	0.257	1.804
AST		0.025	1.068	1.008	1.132	0.338	1.103	0.902	1.349
Albumin		≤0.001	0.051	0.010	0.078	0.056	0.041	0.011	1.139
CEA		0.002	1.512	1.171	1.951	0.987	1.007	0.445	2.279
CA15-3c		0.001	1.160	1.056	1.263	0.178	1.143	0.941	1.389
Cholesterol		≤0.001	1.316	1.019	1.612	0.010	1.312	1.008	1.709
TG		≤0.001	1.070	1.044	1.097	0.001	1.074	1.028	1.123
LDL		0.009	1.308	1.069	1.600	0.110	1.398	0.927	2.106
FNDC5/irisin gene (rs3480)	AA	R	1	-	-	R	1	-	-
	AG	0.219	1.721	0.723	4.100				
	GG	0.024	6.459	1.275	32.692	0.049	5.052	1.182	53.646

OR: odds ratio; CI: confidence interval.

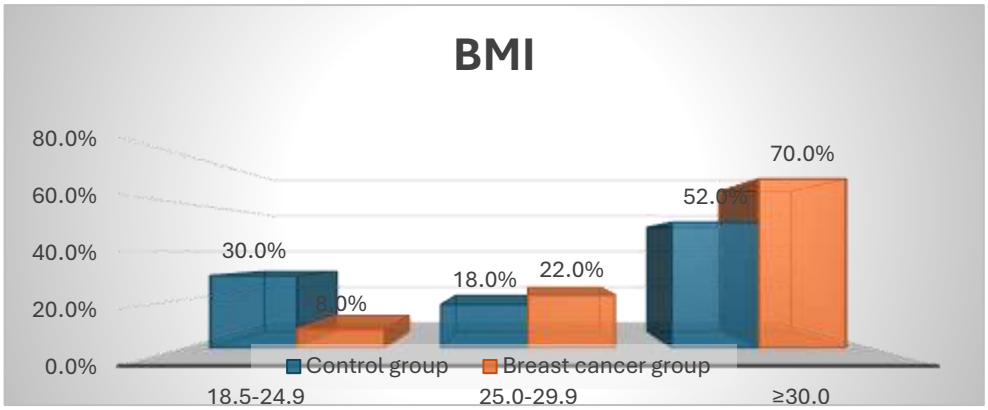

Figure (1): BMI among the studied groups.

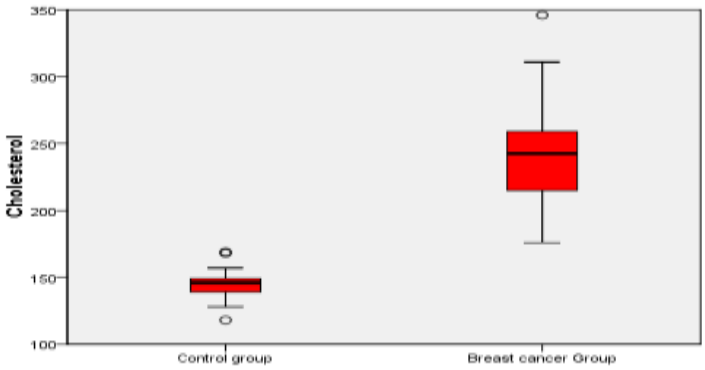

Figure (2): Cholesterol level among the studied groups.

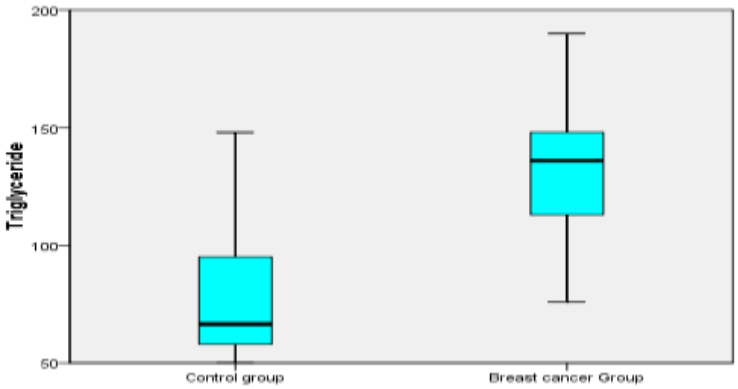

Figure (3): Triglyceride level among the studied groups.

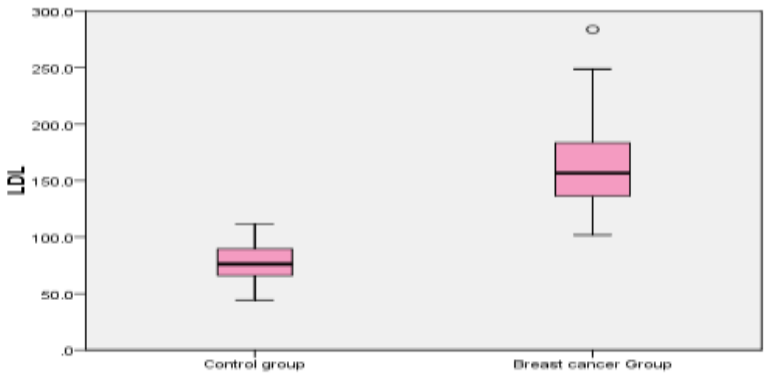

Figure (4): LDL level among the studied group.

4. Discussion

BC is a heterogeneous disease with distinct subtypes characterized by unique epidemiological patterns. Globally, BC accounts for roughly one-third of all malignancies in women, with its mortality rate constituting about 15% of the total number of cases diagnosed (4).

In Egypt, BC comprises the most common of all cancer types in females, with 28,000 confirmed cases each year, as reported by the National Cancer Institute (NCI), Egypt. While the incidence in Egypt seems to be slightly lower than the corresponding rates in the USA and other Western societies, Egyptian BC patients are characterized by a higher mortality rate (20.1 per 100,000) compared to the USA (14.7 per 100,000) (5).

Beyond these molecular classifications, BC can be categorized epidemiologically into familial breast cancer (FBC), hereditary breast cancer (HBC), and sporadic breast cancer (SBC). Approximately 15–25% of BC cases are hereditary, often occurring in women with affected first or second-degree relatives (6). Additionally, cases of FBC in young adults are often inherited. Up to 25% of BC are associated with highly penetrant genes such as BRCA1, BRCA2.

The role of FNDC5/irisin in the occurrence and prevention of cancer has received extensive attention. Irisin has a wide application prospect for cancer treatment (3).

So, this study was carried out to assess the possible association of FNDC5/irisin gene polymorphism (rs3480) with the development of breast cancer.

This study was conducted in Mansoura University, Faculty of Medicine, Clinical Pathology Department. It included 50 BC patients and 50 apparently healthy females matched for age as a control group. 80% of BC patients in this study had IDC, and 40% of them showed distant metastasis. Stage II BC represented the majority of the study patients (38%).

The present study showed a statistically significant increase in BMI in BC patients compared to the control group (P value =0.007). This result agrees with García-Estévez et al., (2025) (7), who stated that obesity has a marked impact on health and, in women, it is associated with an increased risk for many chronic conditions such as diabetes and heart disease. It also results in an increased prevalence of malignancies, including BC. The most recent meta-analysis investigating the role of adipokine levels and BC risk reported that high-risk factors for BC included elevated leptin and lower adiponectin levels. Leptin is tumorigenic, and high levels are associated with BC. Kunyahamu et al.,(2021) (8) reported that obesity increases the risk of developing BC. Fat tissue

only produces a small amount of estrogen, and having more fat tissue can result in a higher estrogen level, which raises the risk of BC.

The current study reported that statistically significant COC administration was more frequent in the BC group compared to the control group (P value =0.012). In agreement with our results, Atroosh et al., (2024) (9) found that women taking COCs had a higher risk of BC than women who had never used the contraceptive pill, and these results were due to increased levels of telomerase. Telomerase activity was significantly present in BC when compared with normal breast tissue or benign breast lesions, and Belachew and Sewasew, (2021) (10) found that the use of hormonal replacement therapy (HRT) can raise the risk of BC, as estrogen increases the risk of BC.

This study showed a significant elevation of cholesterol (P≤0.001), TG (P≤0.001), and LDL (P≤0.001) in the BC group compared to the control group. In agreement with that study Nouri et al., (2022) (11)found that high cholesterol level has been positively related to an increased risk of BC, increased LDL receptor expression in BC tissue, and low HDL-C levels are correlated with an increased risk of BC as biological signaling molecules may affect and modulate cell growth, migration and invasion ability by interacting with cholesterol membrane in BC cells.

The cholesterol-derived sex hormone, such as estrogen, plays a critical role in the development and pathogenesis of BC, but HDL has potential beneficial effect of HDL-raising drugs such as cholesteryl ester transfer protein inhibitor, fibrates, and niacin in treating BC, it may serve as desirable molecules for anticancer drugs delivery, and Reconstituted HDL nanoparticles may directly deliver cytotoxic anti-cancer agents into cytoplasm via HDL receptor.

Wei et al., (2021) (12) found that there is a positive association between blood lipids (especially TC, TG, and LDL-C) and the risk for BC. In general, BC patients with high levels of TG have been reported to show poor prognosis. Apart from the positive association of TG and BC risk, TG is also considered a prognostic factor for recurrence.

There was a significant elevation of AST in BC patients compared to the control group (P=0.017). In accordance with the study results, Aziz et al., (2023) (13) study concluded that BC was associated with elevated AST due to hepatotoxic drugs.

The present study showed a significant reduction of Hb levels in BC patients compared to the control group (P ≤0.001). In agreement with this study results, Al Khamees et al., (2023) (14) reported that iron deficiency anemia and high estrogen levels in premenopausal women can lead to BC due to stimulated production of vascular endothelial growth factor (VEGF).

24 Hypoxia-inducible factor-1α (HIF-1α) is a transcription factor that induces angiogenesis in cancer cells under low oxygen conditions. Iron is a cofactor of prolyl-4-hydroxylase enzyme that degrades HIF-1α and limits the formation of angiogenesis and metastasis. Therefore, iron deficiency can lead to increased HIF-1α expression levels in BC patients, which in return increases VEGF concentration and subsequently angiogenesis.

The results of the present study showed a significant elevation of CEA in BC patients compared to the control group (P ≤0.001). Additionally, the BC group showed significantly higher CA 15-3 levels compared to the control group (P ≤0.001). Similar to our study results, Uygur and Gümüş (2021) (15) reported that CEA and CA 15–3 were significantly higher in BC patients than controls, and their elevations were associated with stage and grade of the tumor. Jiang et al., (2021) (16) found that CEA and CA 15-3 were elevated in non-metastatic BC patients compared with the benign breast diseases (BBD) and controls.

FNDC5 gene (rs3480) polymorphism was studied in control and BC groups, both were in HWE (p=0.857, 0.121, respectively). In this study, analysis of the allele and genotype distribution of

FNDC5 gene (rs3480) polymorphism showed a significant difference between BC and healthy control groups. G allele was statistically significantly higher in BC (p=0.007) vs. control; those with G allele have nearly 2 times higher odds to exhibit BC. FNDC5 gene (rs3480) polymorphism genotypes were also associated with a higher risk effect against BC for those with A/G-G/G genotypes (OR=2.278; 95%CI=1.016-5.108, P=0.045). Those with A/G - G/G genotypes have 2.3 times higher odds of exhibiting BC vs. those with A/A genotype. Also, FNDC5 gene (rs3480) genotypes AG-GG showed a higher risk of distant metastasis and tumor stage compared to AA genotype (P=0.003, ≤0.001, respectively), indicating that, GG genotype could be a risk for BC and G allele could be a risk factor for BC occurrence and bad prognosis of the disease.

Regression analysis was conducted for the prediction of BC from control, using BMI, COC, some laboratory parameters, and FNDC5 gene (rs3480) polymorphism as covariates. Univariate analysis revealed that elevated BMI (OR=1.079; 95%CI=1.019-1.142, p=0.009), COC (OR=3.857;95%CI=1.278-11.638, p=0.017), elevated AST (OR=1.068; 95%CI=1.008-1.132, p=0.025), elevated CEA (OR=0.002; 95%CI=1.171-1.951, p=0.002), elevated CA15-3 (OR=1.160; 95%CI=1.056-1.263, p=0.001), elevated cholesterol (OR=1.316; 95%CI=1.019-1.612, p≤0.001), elevated TG (OR=1.070; 95%CI=1.044-1.097, p≤0.001), elevated LDL (OR=1.308; 95%CI=1.069-1.600, p=0.009), and GG genotype (OR=6.459; 95%CI=1.275-32.692, p=0.024), were significant risk factors for BC. Meanwhile, elevated Hb (OR=0.410; 95%CI=0.256-0.656, p≤0.001) and albumin (OR=0.051; 95%CI=0.010-0.078, p≤0.001) were significant protective factors for BC. Multivariate analysis revealed that elevated cholesterol, TG, and GG genotype were significant risk factors for BC (p=0.010, 0.001, and 0.049, respectively).

The relation between irisin/FNDC5 expression and BC has also attracted a lot of attention. Panagiotou et al.,(2021) (17) reported that higher serum levels of irisin were found in patients with malignant breast lesions than in healthy women. Cebulski et al., (2022) (18) showed that there is an increase in the expression of irisin/FNDC5 in BC compared to the controls.

To the best of our knowledge, this is the first study to assess the FNDC5 gene (rs3480) polymorphism and its association with BC development, but irisin gene expression was studied in many other cancers.

Nowińska et al., (2022) (19) studied the relation between non-small cell lung cancer (NSCLC) and FNDC5 gene and found significantly higher FNDC5 gene expression levels in NSCLCs in comparison to Non-Malignant Lung Tissue (NMLTs). It also found that patients with higher irisin expression in stromal cells had significantly shorter overall survival.

Xu et al., (2022) (20) studied the relation between gastric cancer and FNDC5 gene and found that FNDC5 inhibits the invasion and migration of gastric cancer cells. Furthermore, the risk score model including FNDC5-related genes can be used to predict the prognosis of gastric cancer patients, leading to improved monitoring of the present patient population.

Liu et al., (2021) (21) studied the relation between hepatocellular carcinoma (HCC) and FNDC5 gene expression and found that FNDC5 overexpression in HCC cells affects macrophage phenotypic transformation in the tumor microenvironment and promotes tumor malignant progression.

Zhang et al., (2025) (22) studied the relation between colon adenocarcinoma (COAD) and FNDC5 gene expression and found that Patients with high FNDC5 expression exhibited poorer recurrence and survival rates. FNDC5 could be used as an independent prognostic factor for COAD patients by integrating molecular and clinical features.

5. Conclusion

The present study concluded that there could be an association between FNDC5 gene (rs3480) polymorphism and BC.GG genotype and G allele could be a risk factor for BC occurrence. Elevated BMI levels, AST levels, CEA levels, CA15-3 levels, cholesterol levels, TG levels, LDL levels, and COC intake are significant risk factors for BC development. Elevated Hb and albumin are significant protective factors for BC development.

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