

Influence of *Micro-RNA-423* Gene Variation on Risk and Characteristics of Breast Cancer

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Abstract

Background: *Micro-RNAs (miRNAs)* are post-transcriptional regulators of gene expression that are abundantly expressed in a variety of cancers, including breast cancer. The mechanism of miRNAs in breast cancer oncogenesis is poorly understood. The goal of this study was to determine if there was a link between the *miR-423 rs6505162* gene variation and breast cancer susceptibility among Egyptian patients. **Methods:** This was a case control study that included 120 female patients with pathologically confirmed breast cancer and 120 healthy controls. The patients and controls were genotyped for miR-423 rs6505162 polymorphism by real time PCR. The association of breast cancer patients' genotypic variant and clinicopathological characteristics was analyzed. **Results:** Breast cancer patients showed significantly higher AA and CA genotypes frequencies when compared to controls. This was translated as higher risk to develop breast cancer in patients harboring these genotypic variants (OR = 3.28, p= 0.002; OR = 2.11, p= 0.011, respectively). The frequencies of Her2 positive and advanced stage disease were significantly increased in the AA genotype variant (p<0.001). **Conclusion:** Our data suggest that miR-423 rs6505162 polymorphism could be a potential risk factor in the pathogenesis of breast cancer among Egyptian population.

Keywords: Breast Cancer- micro-RNA- miR-423- rs6505162

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Introduction

Based on GLOBOCAN 2020 data, breast cancer is the fourth malignancy causing mortality worldwide (Sung et al., 2021). The natural history of breast cancer is influenced by many factors with genetic aspects playing a key role. The recognition of the susceptibility genes involved in breast cancer development is substantial and can lead to improvements in diagnosis, treatment, and possible protection from breast cancer (Shiovitz and Korde, 2015).

Micro-RNAs (miRNA) are non-coding RNA molecules that can behave as tumor suppressor genes or oncogenes. More than 1,000 *miRNA* genes are discovered in humans, which regulate the translation or degradation of human messenger RNA (Shivdasani, 2016). MiRNAs are involved in a variety of physiological and pathological processes, including cell proliferation, cell differentiation, cell death, and carcinogenesis, since they regulate about 30% of human genes and can alter the expression of many target genes, including cancer-related genes (Xie and Sadovsky, 2016). More than half of *miRNA* genes are placed in cancer-associated genomic regions or fragile spots and have been identified as oncogenes of many

different types of cancer and found to have essential effect in initiation and progression of cancer (Calin et al., 2004). In this context, miRNA role has been investigated in different types of cancer, in which they act as either a promotor of proliferation or apoptosis (Chang et al., 2016; Li et al., 2017).

Chromosomal instability, epigenetic alterations, genetic mutations, errors in miRNA synthesis pathways, and single nucleotide polymorphisms (SNPs) in miRNA coding genes are all known to affect miRNA expression. (Lee and Dutta, 2009). It is sensible to say that SNPs in *miRNA* genes (MirSNPs) can modify miRNA production, maturation, and their effects on target genes, resulting in altered cellular metabolism and cancer susceptibility (Nicoloso et al., 2010).

MiR-423 gene is located on chromosome 17q11.2 and can generate two mature transcripts, named *miR-423-3p* and *miR-423-5p*. MiR-423 has been shown to play important roles in development, progression, and prognosis of multiple human cancers (Hu et al., 2014). Several results from studies involving breast cancer patients have shown that SNPs in pre-miRNAs, specifically the miR-423 C>A polymorphism, can impact

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the maturation or expression of the relevant mature miRNA (Gyparaki et al., 2014; Zhao et al., 2015). A common C>A polymorphism rs6505162 is located within the pre-miR-423, 12 base pairs 5' of miR-423-5p (Table 1).

The association between the rs6505162 SNP in pre-miR-423 and cancer risk has been evaluated in a range of cancers from diverse populations, including breast cancer, esophageal cancer, hepatocellular cancer, ovarian cancer and bladder cancer, but the findings are still contradictory (Slaby et al., 2012).

To the best of our knowledge, there has been no research to date on the effect of the *miR-423 rs6505162* polymorphism on breast cancer risk in the Egyptian population. As a result, the current study was directed to determine the link between the *miR-423 rs6505162* gene variation and breast cancer susceptibility among Egyptian patients.

Materials and Methods

Study Sample size

The study's minimum sample size was determined to be 102 participants in each group using online sample size calculator (<http://osse.bii.a-star.edu.sg/>) with minor allele frequency of miR-423 rs6505162 (23), level of significant of 5%, and study power of 95%. To adjust for probable dropout, a total sample of 120 subjects was initially intended for each group in the study.

After approval of the local Ethics Committee of Mansoura Faculty of Medicine and obtaining written informed consent from all patients, this study was performed in Oncology Center of Mansoura University in the period between 2020-2021 and all the laboratory investigations were done in the clinical chemistry unit and molecular lab of Oncology Center-Mansoura University.

Study strategy

This was a case control study that included 120 female patients with histopathologically confirmed breast cancer who attended Mansoura Oncology Center, Egypt between July 2020 and December 2021. Another 120 apparently healthy subjects, who attended the blood bank at Mansoura Oncology Center for blood donation, were recruited as controls. The control group was selected to be matched for age and sex with the breast cancer group, with no history of any malignancy, and not related to the patients. Clinical and pathological characteristics of breast cancer patients were gathered from medical health records.

Blood Samples

An approximately 5ml peripheral blood sample was collected from every patient as well as from the healthy controls by venipuncture in EDTA vials. Each sample was divided into 2 parts, first part for laboratory purposes and second part for DNA extraction.

DNA isolation and allelic genotyping of *miR-423 rs6505162*

Genomic DNA was isolated from nucleated WBCs in whole blood using the QIAamp DNA extraction Mini Kit for blood samples (Qiagen, Hilden, Germany). The

quantity and purity of genomic DNA were evaluated using the NanoDrop ND1000 spectrophotometer (NanoDrop Technologies, Inc, Wilmington, DE). Samples were kept at -20°C until analysis.

The TaqMan allelic discrimination polymerase chain reaction (PCR) was used to describe and genotype the intronic variant (rs6505162; C>A) of miR-423 in all the participants (Applied Biosystems). It consisted of oligonucleotides and two probes labeled with a fluorescent dye (either VIC or FAM). Context Sequence was [VIC/FAM]: "TGAGGCCCTCAGTCTTGCTTCCTA[A/C]CCCGCGCTTGAGTTTCTCCCCGCTT".

The protocol used was managed blindly with a final volume of 20 µL containing 5 µL of DNA template (200 ng/µL), 1 µL of TaqMan SNP Genotyping Assay Mix, and 10 µL of TaqMan Universal PCR Master Mix. Thermal cycling conditions were performed as follows: initially, 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds and at 60°C for 30 seconds and final extension was set at 60°C for 2 minutes. In each run, appropriate negative controls were used. About 10% of the samples were chosen at random for assay replication, and the results were 100% concordant. Figure 1 illustrates real time PCR analysis for miR-423 rs6505162

Statistical analysis

Software used

Data were entered and analyzed using IBM-SPSS software (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

Data expression and comparison

Qualitative data were expressed as absolute frequency (N) and relative frequency (%), percentage) and compared by Chi-Square test if the expected counts in all cells were ≥ 5 , if not, Fisher's exact test was used. Quantitative data were initially tested for normality using Kolmogorov test with data being normally distributed if $p > 0.050$. Quantitative data were expressed as median (minimum – maximum) for non-parametric data and mean \pm SD. For two groups, quantitative data were compared by Mann-Whitney U-test for non-parametric data and independent t test for parametric data. For more than two groups, Quantitative data were compared using Kruskal-Wallis H-test for non-parametric data and one way ANOVA for parametric data. Regression analysis with a computation of crude odds ratios (univariable), odds ratios (multivariable), and their 95 % confidence intervals was used to determine the impact of predictor variables on the outcome. The SNPStats online tool (<https://www.snpstats.net/start.htm>) was used to do the SNP analysis. If the P value was less than 0.050 for any of the tests conducted, the findings were considered statistically significant.

Ethical approval

The study protocol including revision of patients' medical records and gathering of written informed consent from all participants was approved by the Mansoura Faculty of Medicine's Institutional Review Board (IRB code: R.20.12.1117).

Results

Pathological characteristics of breast cancer patients

The mean age of participants in the study was 48.43 ± 11.48 years. ER, PR, Her2 were positive in 75.0%, 85.0%, and 53.3% of patients, respectively. Metastasis was detected in 3.3% of patients. TNM staging is presented in Table 2.

Basic characteristics of the studied groups

Comparison of demographic data, and some laboratory parameters among the studied groups yielded significant elevation of TG, cholesterol and LDL levels in breast cancer group compared to controls. On the other hand, there was a significant reduction of frequency of lactation and significant increase of postmenstrual state in breast cancer group. Otherwise, no significant differences could be detected. Data are shown in Table 3.

Assessment of Hardy Weinberg equilibrium for studied miR-423 gene

Participants were chosen at random from the population of Dakahlia Governorate in Delta, Lower Egypt. Applying Hardy Weinberg equation to both breast cancer and control groups revealed that rs6505162 genotypes in the two groups were in HW equilibrium (HWE) as illustrated in Table 4.

Table 1. Genetic Features of Studied SNPs According to National Center for Biotechnology Information (NCBI).

SNP ID	rs6505162
Alleles	C/A
Ancestral Allele:	C
Cytogenetic location	17q11.2
Gene	MiR423
Nucleotide change	C to A substitution at coding region
Amino acid change	-

Distribution of rs6505162 genotype variants and alleles in breast cancer patients versus controls

SNP analysis of genotyping data regarding the risk of breast cancer revealed that the CA genotype was the most common genotype among patients, accounting for 48.3% of cases, while the CC genotype was the most common genotype among healthy controls accounting for 46.7% of controls (Figure 2).

In addition, the genotyping univariate results shown in Table 5, revealed that patients harboring the AA and CA genotypes were at a higher risk to develop breast cancer compared to control (OR = 3.28, 95% CI = 1.56-6.92, $p=0.002$; OR = 2.11, 95% CI = 1.19-3.77, $p=0.011$, respectively). Consequently, a pure link of miR-423 rs6505162 with breast cancer in codominance, and over-dominant patterns was evident.

The overall distribution of common C allele of the miR-423 rs6505162 variant among the study population was 58.7%, whereas the minor A allele frequency was 41.3%. There was a significant association of minor A allele of the miR-423 rs6505162 variant in patients with breast cancer compared to the healthy controls group (49.2% versus 33.3%, $p<0.001$), indicating that A allele could contribute to increased breast cancer risk (OR=1.93,

Table 2. Pathological Characteristics of Breast Cancer Patients

Parameter		N (%)
Mean age in years (\pm SD)		48.43 (\pm 11.48)
ER	Positive	90 (75.0%)
PR	Positive	102 (85.0%)
Her2	Positive	64 (53.3%)
Metastasis	Positive	4 (3.3%)
TNM staging	Stage 1	24 (20.0%)
	Stage 2	70 (58.4%)
	Stage 3	22 (18.3%)
	Stage 4	4 (3.3%)

Dependence of FAM/HEX/ROX/CY5/Cy5.5 channels fluorescence on cycle number

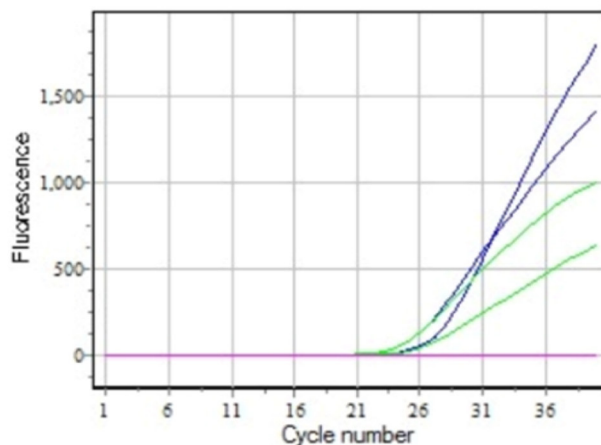


Figure 1. Fluorescence Curves of a Real-Time PCR assay Targeting Analysis for miR423 rs6505162 Polymorphism Indicating 2 CA (Heterozygous) Cases. The used probes are labeled with a fluorescent dye, VIC blue (A allele) and FAM green (C allele)

Table 3. Comparison of Demographic Data, and Some Laboratory Parameters among the Studied Groups

Parameter		Control group (n=120)	Breast cancer group (n=120)	p-value
Age*	Mean ± SD	47.1 ± 11.7	49.6 ± 11.1	0.095
HTN**	Positive	42 (35.0%)	54 (54.0%)	0.114
DM**	Positive	25 (20.8%)	22 (18.3%)	0.626
Family history**	Positive	44 (36.7%)	36 (30.0%)	0.273
OCP**	Positive	78 (65.0%)	66 (55.0%)	0.114
Lactation**	Positive	76 (63.3%)	48 (40.0%)	<0.001
Menstrual state**	Premenstrual	64 (53.3%)	46 (38.3%)	0.02
	Postmenstrual	56 (46.7%)	74 (61.7%)	
BMI	Median (Min-Max)	28.5 (21.0-46.0)	28.9 (21.0-43.0)	0.832
Waist circumference	Median (Min-Max)	87.0 (73.0-120.0)	86.5 (72.0-123.0)	0.051
FBG	Median (Min-Max)	90.5 (57.0-352.0)	97.50 (75.0-165.0)	0.099
TG	Median (Min-Max)	119.5 (61.0-425.0)	172.0 (34.0-420.0)	<0.001
Cholesterol	Median (Min-Max)	188.5 (103.0-323.0)	219.5 (67.0-381.0)	<0.001
HDL	Median (Min-Max)	30.5 (12.0-72.0)	28.0 (12.0-66.0)	0.137
LDL	Median (Min-Max)	95.0 (33.0-223.0)	111.5 (14.0-216.0)	0.009

Independent sample T test*, Chi-Square test**, Mann whitney test; Bold p value indicates significance (p value < 0.05)

Table 4. Assessment of Hardy Weinberg Equilibrium for Studied *miR-423* Genes

Frequency		Control (n=120)		BC patients (n=120)	
		Observed	Expected	Observed	Expected
rs6505162	CC	56	52.5	32	31
	CA	48	55.1	58	60
	AA	16	14.5	30	29
	P (HW)	0.155		0.717	

HW, Hardy Weinberg.

95% CI=1.34-2.80, p <0.001) when compared to the C allele.

Comparison of clinicopathological parameters regarding different miR-423 rs6505162 genotypes in breast cancer patients

We analyzed several clinicopathological parameters in relation to the observed breast cancer genotypes. Our

analysis revealed that there was a significant increase in the frequency of Her2 positive and advanced stage disease (p<0.001) in the AA genotype group. No other significant association was detected among the studied parameters (Table 6).

Prediction of breast cancer from significant covariates
Regression analysis was conducted for prediction

Table 5. Distribution of rs6505162 Genotype Variants and Alleles in All Patients Versus Control.

		Control	Breast cancer patients (n=120)	Relative risk of breast cancer		
		(n=120)		OR	95%CI	
CC	Count	56	32	1	-	-
	%	46.70%	26.70%			
CA	Count	48	58	2.11	1.185	3.771
	%	40.00%	48.30%			
AA	Count	16	30	3.28	1.556	6.92
	%	13.30%	25.00%			
CA+AA	Count	64	88	2.4	1.401	4.131
	%	53.30%	73.30%			
C	Count	160	122	1.93	1.337	2.797
	%	66.70%	50.80%			
A	Count	80	118			
	%	33.30%	49.20%			

OR, odds ratio

Table 6. Comparison of Clinicopathological Parameters Regarding Different miR-423 rs6505162 Genotypes in Breast Cancer Patients

Parameter		CC group (n=32)	CA group (n=58)	AA group (n=30)	p-value
Age*	Mean ± SD	47.9 ± 11.1	49.2 ± 10.2	52.4 ± 12.6	0.266
HTN**	Male	20 (62.5%)	32 (55.2%)	14 (46.7%)	0.456
DM**	Positive	6 (18.8%)	10 (17.2%)	6 (20.0%)	0.949
Family history**	Positive	12 (37.5%)	14 (24.1%)	10 (33.3%)	0.374
OCP**	Positive	20 (62.5%)	32 (55.2%)	14 (46.7%)	0.456
Lactation**	Positive	12 (37.5%)	23 (39.7%)	13 (43.3%)	0.894
Menstrual state**	Premenstrual	14 (43.8%)	20 (34.5%)	12 (40.0%)	0.672
	Postmenstrual	18 (56.2%)	38 (65.5%)	18 (60.0%)	
ER**	Positive	26 (81.2%)	44 (75.9%)	20 (66.7%)	0.406
PR**	Positive	26 (81.2%)	50 (86.2%)	26 (86.7%)	0.785
Her2**	Positive	14 (43.8%)	24 (41.4%)	26 (86.7%)	<0.001
Metastasis**	Positive	0 (0.0%)	2 (3.4%)	2 (6.7%)	0.343
TNM staging**	Early stage (I&II)	26 (81.2%)	52 (89.7%)	16 (53.3%)	<0.001
	Advanced stage (III&IV)	6 (18.8%)	6 (10.3%)	14 (46.7%)	
BMI	Median (Min-Max)	36.0 (22-43)	34.0 (22-42.4)	24.0 (21-40)	0.141
Waist circumference	Median (Min-Max)	93.0 (76-120)	90.0 (72-123)	79.0 (72-119)	0.096
FBG	Median (Min-Max)	98.0 (75-139)	97.0 (79-162)	96.0 (75-165)	0.465
TG	Median (Min-Max)	172.0 (34.0-386)	157.0 (63-420)	193.0 (84-320)	0.566
Cholesterol	Median (Min-Max)	240.0 (67-350)	224.0 (75-381)	199.0 (147-323)	0.538
HDL	Median (Min-Max)	32.15 (12-66)	26.0 (12-56)	30.0 (13-46)	0.403
LDL	Median (Min-Max)	109.0 (14-197)	114.0 (22-216)	116.0 (61-187)	0.436

ANOVA*, Chi-Square test**,Kruskal-Wallis; Bold p value indicates significance (p value < 0.05)

of breast cancer using lactation, menstrual state, TG, cholesterol, LDL, and rs6505162 as covariates. Univariate analysis revealed that postmenstrual, TG, cholesterol, LDL and CA, AA genotypes were significant risk factors for breast cancer, and lactation was significant protective factor. Multivariate analysis revealed that cholesterol and CA, AA genotypes remained significant risk factors for breast cancer and also lactation remained a significant protective factor (Table 7).

Discussion

It is believed that MirSNPs can alter miRNA maturation, silencing, and base pairing at the target site.

Thus, MirSNPs are considered to have essential role in miRNA-mediated gene regulation, which is translated to important effect on susceptibility and progression of many cancers (Slaby et al., 2012). MiR-423 is found within the first intron of the nuclear speckle splicing regulatory protein (*NSRPI*) gene, which is commonly amplified on chromosome 17q11.2. Its pre-miRNA generates two mature transcripts, miR-423-3p and miR-423 5p, which are located at the 3' and 5' termini of the pre-miR-423, respectively. The rs6505162 SNP is found 12 base pairs upstream of miR-423-5p (Kim et al., 2011).

Over-expression of miR-423 have been described in head and neck cancer (Hui et al., 2010), laryngeal carcinoma (Guan et al., 2014), female genital system

Table 7. Logistic Regression Analysis for Prediction of BC from Control

		Univariate analysis			Multivariate analysis				
		p	OR	95% CI	P	95% CI			
Lactation		<0.001	0.386	0.229	0.65	<0.001	0.183	0.592	
Menstrual		0.02	1.839	1.1	3.073	0.067	0.963	3.097	
TG		0.001	1.006	1.002	1.01	0.094	0.999	1.008	
Cholesterol		<0.001	1.009	1.004	1.014	0.003	1.005	1.024	
LDL		0.026	1.006	1.001	1.012	0.089	0.98	1.001	
rs6505162	CC	R	1	-	-	R	-	-	
	CA		0.011	2.11	1.185	3.771	0.003	1.431	5.397
	AA		0.002	3.28	1.556	6.92	0.001	1.862	10.022

OR, odds ratio; CI, confidence interval; logistic regression was used; Non lactating women and premenstrual women are reference group. TG, cholesterol and LDL were introduced as continuous variable in binary logistic regression; Bold p value indicates significance (p value < 0.05)

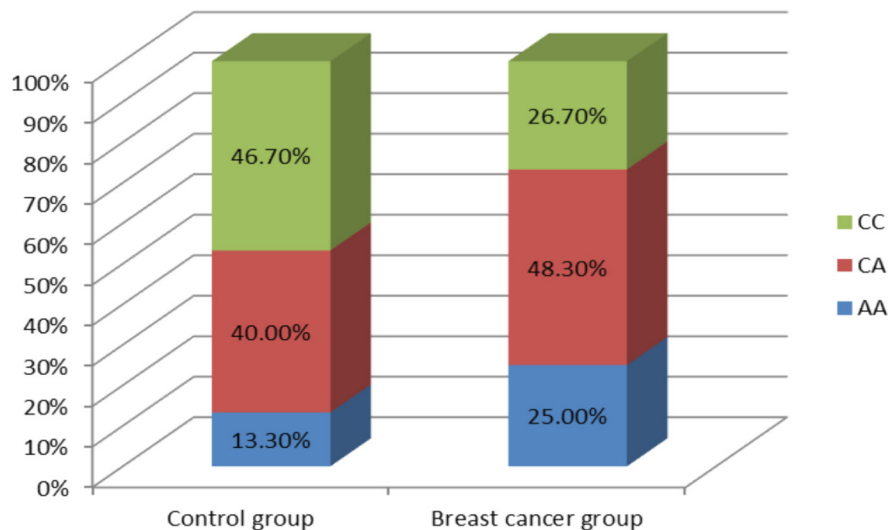


Figure 2. Distribution of rs6505162 Genotype Variants in Patients vs. Controls

tumors (Boren et al., 2008), and digestive system neoplasms (Lin et al., 2011; Ali et al., 2012). Meanwhile, one study showed that miR-423 serves as a tumor suppressor in patients with oral cancer (Roy et al., 2016).

Several studies have been carried out to investigate MirSNPs' actual involvement in precursor and mature miRNA, as well as their impact on carcinogenesis. MirSNPs were linked to the development of cancer in a variety of ethnic groups. A study conducted by Hu et al., (2014) revealed that 9 MirSNPs (including rs6505162/miR-423) were associated with a higher overall risk of various types of cancer. In a study conducted by Ye et al., (2008), they concluded that the C allele of rs6505162 was significantly higher in esophageal cancer patients compared to the controls in the Caucasian population. Another study by Kontorovich et al., (2010) reported that rs6505162 was associated with elevated risk of both ovarian and breast cancer among mutant carriers of Breast Cancer Associated 2 (BRCA2). Moreover, Mir et al., (2018) linked miR-423- rs6505162 polymorphism with an overall increased risk of breast cancer in the Saudi population.

In the present study, we investigated the frequency of miR-423 rs6505162 polymorphism in 120 breast cancer cases and 120 control individuals in the Egyptian population. Our results revealed that breast cancer patients had significantly higher AA and CA genotypes and A allele frequencies when compared to controls. These genotypic variants were identified to remain risk factors having a significant association to breast cancer by multivariate regression analysis. Our results, being in line with previously mentioned studies, revealed that miR-423 rs6505162 polymorphism was associated with increased susceptibility of breast cancer.

In the same context, a study by Smith et al., (2012) showed that the CC genotype of the rs6505162 SNP was associated with decreased risk of breast cancer development with a genotypic shift in breast cancer population towards AA and CA genotypes and a decrease in CC genotype. Interestingly, data reported by Pollard et

al., (2018) pointed out that there is no association between the rs6505162 SNP and breast cancer risk in any genetic model.

In the current study, we revealed that there was significant increase in the frequency of Her2 expression and advanced staging in the AA genotype group, indicating the presence of an association between this polymorphism and poor prognostic factors. This comes in agreement with what was found by Pourmoshir et al., (2020), who noticed an association between miR-423 rs6505162 polymorphism and invasive stages of breast cancer.

On the other hand, some data exist regarding MirSNPs association with decreased cancer susceptibility. One study reported that a genetic variant in pre-miR-27a was associated with reduced risk of breast cancer in Chinese population (Zhang et al., 2013). Similarly, a study by Zhang et al., (2014) identified pri-miR-124 rs531564 and pri-miR-34b/c rs4938723 polymorphisms to be associated with decreased risk of esophageal cancer.

In conclusion, data from our study suggest that miR-423 rs6505162 polymorphism could be a potential risk factor of breast cancer and aggressive tumor biology among Egyptian population. Further studies are necessary to validate our findings and to establish the mechanism by which this SNP affects miRNA function.

Author Contribution Statement

Conception and design: Amira H. El-Ashry and Shimaa R. Hendawy. Collection and assembly of data: Ahmed M. Ramez and Shimaa R. Hendawy. Data analysis and interpretation: Amira H. El-Ashry. Manuscript writing: Ahmed M. Ramez and Ahmed Mamdouh Gaber Albeltagy. Final approval of manuscript: All authors.

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Ethical approval

This study was approved by the Institutional Research Board of Mansoura University, Mansoura, Egypt (IRB code number: R.20.12.1117).

Availability of data

Data are available upon reasonable request to the corresponding author.

Conflict of interest

None.

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