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ORGINAL ARTICLE

Genetic variation in adiposity related genes and risk for breast cancer in postmenopausal women

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ABSTRACT

Background: Breast cancer is the most common malignancy in women and its increasing incidence is a challenge worldwide. Obesity has been linked to an increased risk of developing a number of malignancies, including postmenopausal breast cancer. The link between obesity and breast cancer involves elevated estrogen production and adipokines secretion that affect tumorigenesis.

Objective: We investigated whether genetic variations in the Leptin (LEP) and CYP19A1 genes are associated with risk of breast cancer among Egyptian postmenopausal women.

Methods: This is a case control study. It included 112 postmenopausal breast cancer patients and 112 healthy postmenopausal controls .The LEP(-2548G>A) and CYP19A1 (rs10046C/T) gene polymorphisms were determined using polymerase chain reaction-based restriction fragment length polymorphism and Tetra Amplification refractory mutation system - polymerase chain reaction ,respectively.

Results: Significant difference between postmenopausal breast cancer women and controls regarding allele and genotype distributions of LEP(-2548G>A) (OR 1.8 , 95 % CI 1.23–2.73 and p=0.007 for A allele) and CYP19A1 (rs10046C/T) polymorphisms (OR 1.9, 95 % CI 1.27–3.8, and p = 0.004 for T allele). Moreover, stratified analysis of these polymorphisms in relation to body mass index revealed interactive effect between LEP (-2548G>A) and BMI for the breast cancer risk.

Conclusion: The results suggest that the AA genotype and A allele of leptin polymorphism, as well as the TT genotype and T allele of the CYP19A1 polymorphism, may be associated with increased risk of the development of breast cancer, Moreover obese postmenopausal breast cancer patients carrying LEP A allele have 3 fold risk to develop breast cancer in the Egyptian population.

Keywords: Leptin; adiposity; CYP191A; polymorphism; breast cancer

1.INTRODUCTION

Breast cancer is one of the most invasive cancers and the second leading worldwide cause of cancer-related deaths among women, the pathway of breast tumor genesis is still not completely understood. Many factors are considered to be risk factors for breast cancer such as familial history of the disease, diet, age of menarche and menopause, high estrogen exposure, reproductive history, and genetic factors [1]. The common risk factors elucidate only a minor part of the cases, and liability to breast cancer is determined by a grouping of lifestyle, environmental and genetic factors [2].

Obesity may be linked with breast cancer by estrogen secretion stimulation, which mediated by secretion of leptin and growth factors by adipose stromal stem cells (ASCs)during the postmenopausal period that, in line, promote carcinogenesis[3].Moreover, brown adipose tissue can activate the development of breast cancer by activation of the angiogenesis pathway in mice [4]**.** Menopausal status is the fulcrum on which the complex relationship between obesity and breast cancer hinges. The World Cancer Research Fund reports that there are several evidences supports a possible link between obesity and breast cancer risk in postmenopausal women [5].Polymorphisms which are observed in estrogen synthesis and adiposity-associated genes could increase women tendency to breast cancer [6]**.** Our study included two of the adiposity-related genes: cytochrome P450, family 19, subfamily A, polypeptide 1 (CYP19A1) and leptin (LEP).

Leptin is a hormone arise from adipose tissue, its main role is to modify appetite and energy balance. Cell-based and animal studies have provided strong evidence that leptin plays a role in carcinogenesis [7]**,** and it also involved in increasing the proliferation of breast cancer cell by augmenting estrogen signaling[8]**.**The LEP gene promoter has several binding sites for a multiple transcription factors. The common LEP -2548G>A polymorphism is linked with obesity and alteration in serum leptin levels and leptin synthesis [9]**.**Several studies have investigatethe LEP -2548G>A polymorphism relation to the risk of breast cancer, and the results were inconsistent [10]**.**

CYP19A1 gene (aromatase gene) encode of aromatase which is a key enzyme in estrogen metabolism. CYP19A1 gene polymorphisms have been linked to change the synthesis of estrogen and its activity. This suggests a probable role of CYP19A1 gene polymorphisms in breast cancer initiation and progression [11].Some studies have examined the role of rs10046 SNP, which is a C/T variation found in the 3'untranslatedregion (3'-UTR) of the CYP19 gene, in the risk of breast cancer [12].

Therefore, this study was designed to investigate the potential role of candidate gene variants of CYP19A1 rs10046C/T and LEP -2548G>A polymorphisms and the risk of breast cancer in postmenopausal women and the associations between thesevariants with obesity and breast cancer.

2.SUBJECTS AND METHODS

2.1

This case–control study included 112 postmenopausal breast cancer women evaluated and treated with adjuvant endocrine therapy (aromatse inhibitors),chemotherapy (FAC,FEC,AC+TAXOL weekly) ,and radiation therapy(whole breast irradiation40 Gy/15 fractions in 3 weeks pluse boost to tumor bed 10 Gy /5 fractions in one week or chest wall irradiation 50 Gy /25 fraction in 5 weeks) according to patients stage, pathologic and molecular data in the Clinical Oncology &Nuclear Medicine Department of Zagazig University Hospitals. One hundred and twelve age-matched healthy postmenopausal women were recruited from the same demographic area and taken as controls. Women were considered postmenopausal if they had no menstruation for at least 12 months. Women who had 1ry tumors other than breast cancer, tumors of unknown origin, histopathological diagnosis other than breast carcinoma or advanced liver or kidney diseases were excluded. The study was approved by the ethics committee of Zagazig University and informed consent was obtained from all the subjects included in the study.

The study was done according to The Code of Ethics of World Medical Association (Declaration of Helsinki) for studies involving humans.

All participants assigned informed written consent. They all underwent complete medical history taking including age, menarche, menopause ,family history , taking hormonal therapy and thorough physical examination ,height and weight measurements and assessment of body mass index (BMI) [weight in Kg/surface area in m2].Obesity was defined as body mass index (BMI) 30 kg/m2, consistent withthe World Health Organization (WHO) definition [13]. Clinical characteristics of patient, including tumor size, extension, number of lymph node involvement (TNM stage) , estrogen and

progesterone receptors status, HER2 status ,KI 67 were recorded. Tumor marker level (CA15-3 / CEA), Liver function tests, including (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, albumin), creatinine and complete blood counts were done. Mammography, breast ultrasound ,Chest X-ray , Abdominal and Pelvic US or CT scan when indicated (to exclude Metastasis) were performed ,and bone scan when indicated .

2.2. Laboratory assays

Blood samples were drawn from all subjects after an overnight fast. 1 ml of whole blood was collected into tubes containing EDTA for DNA extraction and stored at -80 °C until genomic analysis.

2.3. Genotyping of-2548 G/A polymorphism in Leptin gene

Genomic DNA was extracted from whole blood using the commercially available G-spin TM Total DNA Extraction Kit (iNtRON Biotechnology, Seongnam, Korea). DNA purity and concentration were determined spectrophotometrically at 260 and 280 nm. The purified genomic DNA was stored at −20 °C until use.

Leptin gene polymorphism was analyzed by polymerase chain reaction amplification followed by restriction fragment length polymorphism (RFLP-PCR) analysis after Hha1 enzyme for 16 h. digestion using forward primer5TTTCCTGTAATTTTCCCGTGAG3 and reserve primer 5AAAGCAAAGACAGGCATAAAAA3 . The PCR was performed in a final volume of 25 µl containing 100 ng of template DNA, 0.5 µM of each primer (Biosearch Technologies), and 12.5 µl of 2X i-TaqTMPCR Master Mix (iNtRON Biotechnology). The amplification was carried out using DNA thermal cycler 480, PERKIN ELMER (Norwalk, CT 06856, USA). Cycling conditions were initial denaturation of 94°C for 4 minutes, followed by 40 cycles of 94 °C for 30 sec., 58° C for 30 sec. and 72°C for 30 sec. Final extension of 72°C for 10 minutes.The PCR products were digested using Hha1 (New England Biolabs) restriction endonuclease. The digestion was performed in a total volume 25µl containing 15µl of PCR Product, 2µl of enzyme Hha1, 2.5µl of 10X buffer and 5.5µl of nuclease-free water. The digested PCR product samples were incubated at 37°C for 16 hours. The PCR products were separated in a 3% agarose electrophoresis system, then visualized with ethidium bromide staining under UV transillumination with 100-bp SiZer TM DNA marker (iNtRON Biotechnology) .The presence of only one band of 241bp length indicated individuals with GG homozygous genotype, the presence of three bands of 241bp, 181bp, and 60bp length indicated individuals with GA heterozygous genotype, and the presence of two bands of 181bp and 60bp length indicated individuals with AA homozygous genotype.

2.4. Genotyping of rs10046 Polymorphism of Aromatase (CYP19) gene

The protocol used for DNA extraction from whole blood is the same of what used in detection of leptin gene polymorphism .Tetra Amplification refractory mutation system - polymerase chain reaction (T-ARMS-PCR) assay was used for detection of CYP191A (rs10046) polymorphism as described by Piccioli et al[14]using the following primers: Forward outer: 5´- CAG AAGATACA GACTTG TCCTTGCACCCAG -3´Reverse outer: 5´- CCGACTATT TCTCCCTCAAACTCTTGGC- -3´Forward inner: 5´-CCGACTATTTCTCCCTCAAACTCTTGG C -3´ (for C allele)Reserve inner:5´-CTGGAACACTAGAGAAGGCTGGTCAG TAGCC3´(for T allele).Cycling conditions were initial denaturation of 94°C for 4 minutes, followed by 40 cycles of 94 °C for 30 sec., 58° C for 30 sec. and 72°C for 30 sec. Final extension of 72°C for 10 minutes, then Samples were loaded on agarose gel and electrophoresis was performed.

2.5. Statistical analysis

Data were processed using the Statistical Package for Social Science version 13 (SPSS Inc., Chicago, IL). The ages of the patients and the controls were compared by the Student t test. The chi-square test was used to test the association between the genotypes and alleles in relation to the cases and controls, and to test for deviation of genotype distribution from the Hardy–Weinberg

equilibrium (HWE). The odds ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated to estimate the strength of the association between polymorphism genotype alleles of patients and controls. A value of $p<0.05$ was considered statistically significant.

3. RESULTS

The demographic data of studied groups were described in Tables 1. There was no significant difference between the two groups regarding age (P= 0.187).but there was significant difference between the two groups regarding BMI (P= 0.009).

The clinical and pathological characteristics of the breast cancer patients stratified according to the LEP -2548G>A and CYP19A1C/T polymorphisms are shown in (table 2,3) . No association was observed between LEP -2548G>A and CYP17A1 T27C genotypes and clinical and pathological characteristics, except for leptin and BMI.

3.1. Leptin -2548 G/A polymorphism analysis and breast cancer risk

The genotype frequencies were in accordance with the HWE among the controls (P = 0.72) and among the patients (P = 0.63).In control group , the frequencies of GG, GA, AA genotypes were 51.7, 42.8 and 5.5%, respectively, and in Patients group , the frequencies were 37.5, 44.6, and 17.9 %, respectively. Chi-square revealed significant difference regarding the distribution of LEP genotypes AG and AA between patients and control (P=0.008). As regard the risk of development of breast cancer, the increased AA genotype frequency was significantly associated with an increased risk of breast cancer (OR = 4.6, 95% CI 1.6–12.4, and P = 0.0008). The increased A allele carriage was significantly associated with increased risk breast cancer (OR = 1.8, 95% CI = 1.23-2.73), and P = 0.007)(table 4).

. CYP191A rs10046 C/T polymorphism analysis and breast cancer risk

The genotype frequencies were in accordance with the HWE among the controls (P = 0.28) and among the patients (P = 0.87).In control group , the frequencies of CC, CT, TT genotypes were 50 , 46.4 and 3.6 %, respectively, and in Patients group , the frequencies were 35.7 , 46.4 , and 17.9%, respectively Chi-square revealed significant difference regarding the distribution of CYP191A genotypes CT and TT between patients and control (P=0.000) As regard the risk of development of breast cancer, the increased TT genotype frequency was significantly associated with an increased risk of breast cancer (OR = 5.87, 95% CI 1.8–9.11, and P = 0.02). The increased T allele carriage was significantly associated with increased risk breast cancer (OR = 1.9 , 95% CI = 1.27-3.8, and P = 0.004)(table 4).

When we stratified the control and cases according to BMI into two groups each group included those who have BMI less than 30kg/m^2 and the other group those who have BMI more than 30kg/m^2 · Obese postmenopausal breast cancer patients carrying LEP A allele have 4 fold risk to develop breast cancer (OR:3.02 , 95% CI: 1.49-6.78) (table 5).

When we stratified the control and cases according to BMI into two groups each, group included those who have BMI less than30 kg/m^2 and the other group those who have BMI more than 30kg/m^2 · Obese postmenopausal breast cancer patients carrying T allele don't have considerable risk to develop breast cancer (OR: 1.04, 95% CI: 0.58 to 2.127) different from normal weight postmenopausal breast cancer patients carrying T allele (OR: 2.08,95% CI: 0.92 - 4.6)(table 6)

Table (1): Demographic data of the studied groups.

		Control group	Patients group	P-value
		No. = 112	No. = 112	
Age	Mean ± SD	55.74 ± 3.28	56.84 ± 6.00	0.187
	Range	50–64	45–68	
BMI	Mean ± SD	30.05 ± 4.73	33.07 ± 6.60	0.006
	Range	24.51 – 42.46	21.08–47.87	

Table 4: Genotype distributions and allelic frequencies of *Leptin-2548 G/A and CYP191A rs10046C/T* polymorphism in breast cancer patients and controls

		Control group	Patients group	Chi-square test		OR (95% CI)	Sig.
		No. (%)	No. (%)	X^2	P-value		
Leptin gene	AA	6 (5.5%)	20(17.9%)	14.11	0.0008	4.6 (1.6 to 12.4)	HS
	AG	48 (42.8%)	50(44.6%)			1.4 (0.8 to 2.5)	S
	GG	58 (51.7%)	42(37.5%)			*Ref*	*Ref*
Leptin gene	GG	58 (51.7%)	42(37.5%)	13.87	0.000	*Ref*	*Ref*
	AA & AG	54 (48.2%)	70(62.5%)			1.79 (1.02 to 3.16)	HS
Leptin allele	A	60 (26.7%)	90(40.1%)	7.236	0.007	1.8 (1.23 to 2.73)	HS
	G	164(73.3)	134(59.9%)			*Ref*	*Ref*
Cyp gene	CC	56 (50%)	40(35.7%)	17.74	0.000	*Ref*	*Ref*
	CT	52(46.4%)	52(46.4%)			1.01(0.57 to 7.75)	NS
	TT	4 (3.6%)	20 (17.9%)			5.87 (1.8 to 9.11)	S
Cyp gene	CC	56 (50%)	40(35.7%)	10.5	0.001	*Ref*	*Ref*
	CT & TT	56(50%)	72(64.3%)			1.81 (1.03 to 3.25)	S
Cyp allele	C	164(73.2%)	132(58.9%)	7.966	0.004	*Ref*	*Ref*
	T	60 (26.8%)	92 (41.1%)			1.9 (1.27 to 2.8)	HS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Table(2):Clinical and pathological characteristics among breast cancer patients according to genotypes of leptin gene polymorphism

			Leptin gene			X2	P
			AA	AG	GG		
Stage	I	N	1	0	0		
		%	5 %	0.0%	0.0%		
	II	N	9	28	21		
		%	45.0%	56.0%	50.0%		
	III	N	8	20	21	7.68	0. 12
		%	40%	40.0%	50.0%		
	IV	N	2	2	0		
		%	10%	4.0%	0.0%		
ER	Negative	N	0	0	2		
		%	0.0%	0.0%	4.8%		
	Positive	N	20	50	40	4.29	0.11
		%	100.0%	100.0%	95.2%		
PR	Negative	N	8	20	21		
		%	40.0%	40.0%	50.0%		
	Positive	N	12	30	21	2.34	0.31
		%	60.0%	60.0%	50.0%		
HER2	Negative	N	12	25	12		
		%	60.0%	50.0%	28.5%		
	Positive	N	8	25	30	3.87	0.13
		%	40.0%	50.0%	71.5%		
BMI	< 30	N	14	18	20		
		%	70.0%	31.0%	47.2%		
	> 30	N	6	32	22	6.67	**0.036***
		%	30.0%	69.0%	52.8%		
Diagnosis	Bilateral breast cancer	N	3	8	7		
		%	15.0%	16.0%	16.7%		
	Unilateral Breast cancer	N	17	42	35	0.88	0.61
		%	85.0%	84.0%	83.3%		
Total		N	20	50	42		
		%	100.0%	100.0%	100.0%		

Table(3):Clinical and pathological characteristics among breast cancer patients according to genotypes of *CYP191A rs10046C/T* polymorphism

			Cypgene			X^2	P
			CC	CT	TT		
Stage	I	N	0	1	0		
		%	0.0%	1.9%	0.0%		
	II	N	20	30	8		
		%	50.0%	57.%	40.0%		
	III	N	20	18	11	4.89	0.46
		%	50.0%	34.6%	55.0%		
	IV	N	0	3	1		
		%	0.0%	5.8%	5.0%		
ER	Negative	N	0	2	0		
		%	0.0%	3.8%	0.0%		
	Positive	N	40	50	20	2.03	0.36
		%	100.0%	96.2%	100.0%		
PR	Negative	N	15	22	12		
		%	37.5%	42.3%	60.0%		
	Positive	N	25	30	8	3.25	0.18
		%	62.5%	57.7%	40.0%		
HER2	Negative	N	15	28	6		
		%	37.5%	53.8%	30.0%		
	Positive	N	25	24	14	7.25	0.18
		%	62.5%	46.1%	46.6%		
BMI	< 30	N	19	20	9		
		%	47.5%	38.4%	45.0%		
	> 30	N	21	32	11	0.87	0.67
		%	52.5%	61.5%	55.0%		
Diagnosis	Unilateral Breast cancer	N	36	46	12		
		%	90.0%	88.5%	60.0%		
	Bilateral breast cancer	N	4	6	8	10.3	0.075
		%	10.0%	11.5%	40.0%		
Total		N	40	52	20		
		%	100.0%	100.0%	100.0%		

***Table (5):*Association between Leptin genotype and BMI for the risk of breast cancer.**

BMI	Genotype	Control group	Patients group	OR (95% CI)
		No. (%)	No. (%)	
<30	AA+GA	34 (63%)	32 (45.7%)	1.08 (0.5 to 2.3)
	GG	23 (40%)	20 (47.6%)	*Ref*
>30	AA+GA	20(37%) 35 (60%)	38 (54.3%) 22(52.4%)	***3.02 (1.49 to 6.78)****
	GG			*Ref*

***Table (6):*Association between *CYP191A* genotype and BMI for the risk of breast cancer**.

BMI	Genotype	Control group	Patients group	OR (95% CI)
		No. (%)	No. (%)	
<30	CC	30 (53.6%)	19(47.5%)	Ref
	TT+ CT	22(39.2%)	29 (40.3%)	2.08 (0.927to 4.62)
>30	CC	26 (46.4%)	21 (52.5%)	*Ref*
	TT+ CT	34 (60.7%)	43 (59.7%)	1.04 (0.58 to 2.127)

4.DISSCUSION

Breast cancer is a malignancy that threatens women's life. In Egypt, breast cancer is representing 38.8% of total cancer cases in females [15]**.** Breast cancer etiology is highly heterogeneous in terms and pathological characteristics, There are cases showing slow growth with excellent prognosis, while others representing a highly forceful clinical course [16]**.** The etiology is still poorly understood with known breast cancer risk factors explaining only a small proportion of cases [17]

Many gene polymorphisms of receptors , enzymes and ligands are possibly related to carcinogenesis have been investigated for breast cancer risk, but only few have revealed positive associations, Polymorphisms which are detected in adiposity-related genes could influence circulating estrogen and adipokine levels and affect a woman's predisposition to breast cancer [18].

According to the literature, LEP gene mutations are associated with cancer in humans. It has been revealed recently that leptin and its receptor may play a role in the initiation and progression of breast cancer [19]**.**Many studies hasexplained strong evidence for a participation of leptin in breast cells stimulation, proliferation, ,angiogenesis,and cell migration [20]. A meta-analysis of **Niu et al** showed that the leptin level plays a role in breast cancer and has potential for development as a diagnostic tool [21]. Several polymorphisms in leptin gene have been related to breast cancer, such as -2548 G/A, because this polymorphism in the promoter of leptin gene can affect the expression of this gene [22].

The results of current study reported a seven fold increase in risk of developing breast carcinoma for those who carried the LEP-2548AA genotype (OR = 4.6; 95% CI = 1.6–12.4), compared with women who were homozygous for the LEP -2548 G allele .Results of the present study were with- **Liu etal**.[23]. who suggested that the A allele of leptin G-2548A polymorphism may be a determinant of cancer development**.** Also,,it was reported that the LEP -2548G>A polymorphism could cause leptin over-expression in breast cancer cells [24].

A recently published meta-analysis showed that the Leptin-2548G/A gene polymorphism was associated with overall cancer and A>G variant had a significantly increased risk of breast cancer in overall population [25].

In a study by **Fan and Say**, there was no significant association between -2548 G/A LEP polymorphism, with the breast cancer risk [26]**.**A meta-analysis comprising 3 studies that investigate the association between LEP -2548G>A and breast cancer risk failed to show a significant association [10]. The differences in the findings of similar studies with the present study can be due to racial differences, various genetic polymorphisms in similar metabolic pathways (gene-gene interaction) and environmental factors (e.g., stress)that may affect leptin expression .We can settle that genetic correlation is population dependent and shows different results in different populations [27].

An increase in estrogen signaling involves in breast carcinogenesis [28]. Consequently, variants which can change the levels of estrogen have been investigated in different populations to reveal its association with

breast cancer [29]. CYP19A1 is one of the important enzymes involved in estrogen biosynthesis. Genetic variation at this gene may alter aromatase activity and thereby affect hormone levels. The CYP19 polymorphism rs10046 been related to the levels of estradiol and the estradiol: testosterone ratio in normal postmenopausal women, a parameter that significant for breast cancer development [30]. A Chinese study has demonstrated that the CYP19 rs10046 polymorphism is linked with breast cancer risk among Chinese women [31]. **Karin et al.** found that the rs10046 T-allele of the CYP19 gene is associated with a "high activity" phenotype and that the TT genotype of this polymorphism was associated with increased breast cancer risk [30]. Similar to that study, present data suggest that the TT genotype has a tendency to be overrepresented in patient group than control .The current results show that there was five fold increase in risk of developing breast carcinoma for those who carried the TT genotype (OR = 5.87; 95% CI = 1.8-9.11), compared with women who were heterozygous CT or homozygous CC for the rs1006.

Several hypotheses have been explained the possible linkage of obesity with postmenopausal breast cancer. One hypothesis is the elevated estrogens levels arising from peripheral aromatization of androgens in adipose tissue in obese postmenopausal women [32]. A newer hypothesis places adipocytes and their autocrine, paracrine, and endocrine functions at center stage,Leptin and adiponectin are two major adipocyte-secreted hormones. The pro-carcinogenic effect of leptin and the anti-carcinogenic effect of adiponectin represent two main mechanisms in breast carcinogenesis[33].

Results of the present study revealed that increase body mass index BMI was significantly associated with breast cancer risk, this result was in agreement with **Chan et al.,2014 and Playdon et al.,2015**[34][35]who showed strong association between obesity and the risk of breast cancer.The current results revealed interactive effect between LEP (-2548G>A) and BMI for the breast cancer risk. Obese postmenopausal breast cancer patients carrying LEP A allele have 3 fold risk to develop breast cancer (OR: 3.02 , 95% CI: 1.49-6.78) .Our result goes with Luz et al who detected an association between LEP (-2548G>A) and BC in obese postmenopausal women[36]. Rebecca et al reported that variant in the promoter region of the LEP gene at locus -2548 is associated with a 30% increase in risk of breast cancer development, and the association may be more profound among obese women. [37]. Regarding CYP 191A gene polymorphism, There was no association between CYP191A genetic polymorphism and BMI for the breast cancer risk.

Finally, interpretation of the present results should be viewed in light of some limitations. First, the sample size was relatively small. Second, ethnic differences consider important factor could affect this type of genetic studies. Third, breast cancer is a complex disease, including interactions among gene–gene and gene–environment. It is a challenge to create a mechanistic correlation between a particular allele and a disease.

In conclusion, despite these limitations of this study to a limited population, the current results support the hypothesis that LEP gene polymorphism in postmenopausal females carrying A allele are more susceptible to breast cancer. Post-menopausal women who carried the variant A allele and were obese were at an increased risk of breast cancer. The current results support also the hypothesis that Aromatase gene polymorphism in postmenopausal females TT genotype of the rs10046 polymorphism in the CYP19 gene is associated with a higher relative breast cancer incidence.

Conflict of Interests:

The authors declare that there is no conflict of interests regarding the publication of this paper.

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