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Abstract

Contradictory results were reported on the effect of fat mass- and obesity-associated (FTO) gene and anthropometric measurements on breast cancer (BC). This study aimed to assess the interactions between rs9939609 polymorphism of FTO gene, anthropometric indices and BC risk in Iranian women. This case-control study was performed on 540 women including 180 women with BC and 360 healthy women in Tehran, Iran. Physical activity and dietary intakes were assessed by validated questionnaires. Data on sociodemographic and pathologic factors of the participants as well as their blood samples were collected. The rs9939609 FTO gene polymorphism was genotyped using the tetra-primer amplification refractory mutation system-polymerase chain reaction (T-ARMS-PCR). No significant association was found between BC and risk allele of FTO rs9939609 polymorphism after adjustments for the confounders. However, there was a significant association between rs9939609

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which is responsible for 1 million of about 10 million new neoplasms which are diagnosed every year around the world.[1-4] The prevalence of BC is increasing which may be partly due to lifestyle issues and the obesity pandemic.[3,5] Early menstruation, late menopause, having the first child at an older age, smoking, hormonal replacement therapy, contraceptive medications and lack of breastfeeding have all been identified as the risk factors for developing BC.[6,7] Furthermore, dietary intake,[5] obesity and anthropometric indices are the other important factors associated with BC.[8] Obesity has been consistently associated with an increased risk of postmenopausal breast cancer in population-based studies. Conversely, obesity in such studies has been inversely associated with premenopausal breast cancer risk.[9]

Fat mass- and obesity-associated (FTO) gene have been reported to play an important role in the aetiology of both obesity and BC.[9,10] FTO gene is expressed in different human tissues[11] and plays a role in the regulation of cell metabolism.[12] The expression of FTO is reported to be regulated by dietary intake and nutritional status.[13,14] Many studies have also reported a significant association between FTO genotype and anthropometric measurements such as body mass index (BMI), body weight and body composition.[15] For example, the carriers of the A allele of FTO rs9939609 polymorphism have a higher body fat percentage.[16-18] The homozygotes for the FTO rs9939609 risk allele (A) had higher serum leptin,[16] and the amounts of dietary calorie, carbohydrate and fat intake were associated with FTO genotype.[17] The obesity-related SNPs reside in the first intron of FTO, and they may not only impact FTO but mediate their obesity effects via nearby genes such as IRX3.[18]

On the other hand, recent studies have reported that there is a strong association between FTO single nucleotide polymorphisms (SNPs) such as rs9939609 with the increased risk of some types of BC, implying a possible mediatory role of FTO in the pathogenesis of cancers.[10,19] The FTO may act as an amino acid sensor, linking other related factors on this association. Moreover, the association between anthropometric indices and cancer has been frequently reported.[8,24] However, the effect of anthropometric indices on the manifestation of the effect of the FTO risk allele on BC is not yet clear. Based on the previous studies,[9,16] body weight and BMI may influence the effect of FTO gene on the risk of BC.

Given the high prevalence of BC and inconclusive results of studies, this case-control study was aimed to identify the interactions between anthropometric indices, FTO gene rs9939609 polymorphism and BC risk in Iranian women.

2 | METHODS

2.1 | Study population and data collection

A case-control study was performed on 540 adult women including 180 patients with cancer as the case group and 360 healthy individuals as the control group. A 1:2 case-to-control ratio was used in this matched case-control study due to concern for sufficient numbers in stratified analysis and increase in power given the expected prevalence of exposure among the controls. The required sample size was estimated according to a previous similar study.[10] The cases were selected according to the inclusion criteria from adult women referring to the Cancer Research Center of Shohada Tajrish Hospital in Tehran, Iran. The controls were selected from the adult women who participate in Sabzevar Persian cohort study. The inclusion criteria for the case group included females with BC, age between 35 and 70 years, consent to participate in the study, lack of diseases affecting body weight, do not take drugs that affect body weight and not more than 3 months after the BC diagnosis. The inclusion criteria of the control group included females with no malignancy, age

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Height was measured using a stadiometer. The patient's weight was measured using a SECA Alpha 882 scale (SECA Corporation). The patients' BMI was then calculated by dividing the weight by the square of height.

2.4 | Statistical analysis

The two groups were compared in terms of demographic, anthropometric, clinical indicators and the presence of FTO gene polymorphism at the beginning of the study using t test (for quantitative variables) and chi-square (for qualitative variables) methods. Then, the relationship between BC and the risk allele of rs9939609 polymorphism (the dominant genetic model) was investigated using the logistic regression method.

The effects of confounding variables were adjusted using different models in the logistic regression method including age, family history of BC, menopausal status, lactation time, history of abortion, age of onset of menstruation, number of pregnancies and BMI model 1, and further adjustments for smoking, alcohol consumption, calorie intake, macronutrients intake and physical activity in Model 2. In the next step, to investigate the effect of BMI on the relationship between FTO gene polymorphism and BC risk, statistical analysis was limited to overweight people (BMI > 27). All statistical analyses were performed using SPSS software ver. 21.0 (IBM) and considering the significance level of $P < .05$.

3 | RESULTS

The mean BMI of the cases and controls was 29 (±2.8) and 27 (±2.3), respectively ($P < .01$). In the case group, the rate of

TABLE 1 Characteristics of the participants

	Cases (170)	Controls (360)	*P*
Age (y)	68 (±29)	65 (±27)	.06
Height (cm)	156 (±5)	161 (±6)	.01
Weight (kg)	71 (±11)	71 (±10)	.86
BMI (kg/m^2)	29.19 (±2.8)	27.27 (±2.3)	.01
Breastfeeding duration (mo)	34 (±29)	59 (±33)	.01
First menstruation age (y)	13 (±2)	13 (±2)	.51
Menopausal age (y)	47 (±5)	47 (±5)	.89
Menopausal women	110 (65%)	223 (62%)	.66
Family history of BC	60 (35%)	50 (14%)	.01
Number of pregnancies	3 (±2)	4 (±2)	.01
Smoking	5 (2.9%)	18 (5%)	.34
Using alcohol drinks	168 (98.5%)	357 (99.2%)	.62
Physical activity (h/d)	2 (±4.5)	1.5 (±1.5)	.51
FTO genotype for rs9939609 polymorphism			
TT	22 (31%)	126 (35%)	.79
AT	19 (11%)	32 (9%)	
AA	99 (58%)	202 (56%)	
Dominant model			
TT	53 (31%)	126 (35%)	.46
AA + AT	117 (69%)	234 (65%)	
Calorie intake (Kcal)	2737 (±925)	2315 (±106)	.01
Protein intake (g/d)	87 (±42)	85 (±42)	.81
Carbohydrate intake (g/d)	402 (±125)	312 (±170)	.01
Fat intake (g/d)	92 (±42)	75 (±31)	.25

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ing smoking, alcohol consumption, macronutrients intakes and physical activity, this association was disappeared (Table 4). These results indicated that the FTO gene polymorphism may be associated with the risk of BC in overweight people and probably exert its effects through changes in lifestyle factors including diet, alcohol consumption and smoking.

4 | DISCUSSION

The present case-control study found no significant association between BC and risk allele of FTO rs9939609 polymorphism in the participants with different BMI, in line with some previous studies.[20,22] For example, Mojaver et al found no significant association between rs9939609 FTO gene and the risk of BC among Iranian women.[21] Also, Da Cunha et al found no association between this polymorphism and BC risk.[23] On the other hand, Kaklamani et al and Zhao et al identified a significant association between several SNPs of the FTO gene including rs9939609 with the BC risk.[10,25] These

TABLE 2 Logistic regression of the association between risk allele of rs9939609 FTO gene polymorphism and BC in all participants

Model	SE	OR	*P*
Model 1	0.25	1.21	.46
Model 2	0.31	1.24	.50
Model 3	0.54	2.05	.18

Note: Model 1: crude. Model 2: adjusted for age, family history of BC, postmenopausal status, months of breastfeeding, number of abortion, first menstruation age and the number of pregnancy. Model 3: further adjustments for smoking, alcohol, calorie and macronutrient intakes and physical activity.

Postmenopausal age (y)	45 (±5)	47 (±5)	.06
Family history of BC	46 (38%)	34 (14%)	.01
Number of pregnancies	3 (±1.8)	3 (±1.9)	.15
Smoking	4 (3%)	2 (1%)	.13
Using alcohol drinks	117 (97.1%)	242 (98.8%)	.45
Physical activity (h/d)	2.5 (±6.2)	1.5 (±1.4)	.01
FTO genotype for rs9939609 polymorphism			
TT	13 (10.5%)	86 (35%)	.16
AT	95 (79%)	132 (54%)	
AA	13 (10.5%)	27 (11%)	
Dominant model			
TT	13 (10.5%)	86 (35%)	.03
AA + AT	107 (89.5%)	159 (65%)	
Calorie intake (Kcal)	2847 (±1034)	2267 (±936)	.01
Protein intake (g/d)	92 (±48)	80 (±33)	.18
Carbohydrate intake (g/d)	409 (±152)	307 (±136)	.01
Fat intake (g/d)	99 (±50)	90 (±47)	.36

TABLE 4 Logistic regression of the association between rs9939609 FTO gene polymorphism and BC in overweight participants

Model	SE	OR	*P*
Model 1	0.76	4.5	.04
Model 2	1.60	4.10	.04
Model 3	0.23	4.01	.98

Note: Model 1: crude. Model 2: adjusted for age, family history of BC, postmenopausal status, months of breastfeeding, number of abortion, first menstruation age and the number of pregnancy. Model 3: further adjustments for smoking, alcohol, calorie and macronutrient intakes and physical activity.

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is plausible that the association between FTO gene and lifestyle is a mutual connection. The FTO gene polymorphisms can affect our food intake and physical activity. On the other hand, nutrient intake and physical activity may affect FTO gene expression level.[17-19]

Several studies have confirmed the association of alcohol consumption and smoking with the FTO gene and indicated that alcohol consumption and smoking are affected by the rs9939609 polymorphism of the FTO gene.[30,31] However, Hubacek et al found no association between this polymorphism and alcohol consumption. A recent study indicated that the effect of FTO polymorphisms on alcohol consumption may be altered under different environmental conditions.[32]

However, there were some limitations in our present study. First, different types of BC including the status of hormone receptors and also the stage of BC were not considered. Second, other anthropometric measurements such as persons' body fat were not assessed. Third, this study was limited to only one SNP of the FTO gene and other SNPs may have different associations with BC. Finally, the participant was not categorized based on their menopausal status and further studies are warranted.

5 | CONCLUSION

In general, this case-control study did not find any significant association between FTO gene polymorphism and BC. The FTO rs9939609 polymorphism risk allele was associated with the risk of BC in overweight people. However, adjustments for lifestyle factors including smoking, alcohol consumption, macronutrients intakes and physical activity disappeared the association. Further studies on the patients with different types of BC are needed to assess the possible effects of the FTO genotype on BC risk.

JavadiKooshesh: Methodology (equal). **Ghasem Azizi Tabesh:** Investigation (equal). **Fatemeh Montazeri:** Visualization (equal). **Parvin Joola:** Methodology (equal); Validation (equal). **Shahla Rezaei:** Data curation (equal). **Masoomeh Dorosti:** Methodology (equal); Supervision (equal). **seyed Alireza Musavi Jarrahi:** Formal analysis (equal); Funding acquisition (equal).

DATA AVAILABILITY STATEMENT

The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the ethics committee of Sabzevar University of Medical Sciences and Health Services (Reference Number: IR.MEDSAB.REC.1397.070), Khorasan Razavi, Iran. All participants involved provided written informed consent form before joining the project.

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