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REVIEW

Meta-analysis of Studies Investigating Association between FTO Gene Polymorphisms and Breast Cancer

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Abstract

Back Objectives: The aim of this study is to pool the result of studies on the association between FTO gene polymorphisms and breast cancer (BC). **Material and Methods:** We searched PubMed, Embase, Science Direct, Scopus, web of science, and Cochran to identify studies investigating the associations between the rs1477196 and rs9939609 polymorphisms and BC risk. We pooled adjusted odds ratios (ORs) as overall. ORs were estimated using a random effects model. **Results:** In total, 16 articles were included in the final analysis. Considering the dominant model of inheritance, there was an inverse association between the rs1477196 polymorphism and BC (OR 0.76 [0.64- 0.91]). There was not observable heterogeneity (I2: 0.0%, P=.867), but with a small study effect (b=1.19, P=.03) in this analysis. Moreover, there was not any association between the rs9939609 polymorphism and BC (OR 0.98 [0.79- 1.2]). There was not observable heterogeneity (I2: 23.1%, P=.27) and small study effect (b=-3.817, P=.303) in this analysis. **Conclusions:** The carriers of rs1477196 polymorphism of FTO are at lower risk for BC. Carriers of Rs9939609 polymorphism had no association with Breast cancer risk.

Keywords: FTO gene- Breast Cancer- Polymorphism

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Introduction

Obesity increases the risk of breast cancer by 30-50% in women after menopause [1]. In a 16-year cohort study on 900,000 healthy people, obesity caused 57,000 cancer related deaths. Additionally, it has been shown that the death rate from cancer in persons with the highest BMI was twice that of women with the lowest BMI [2]. Genetic, behavioral and environmental factors are among the most important factors associated with both obesity and breast cancer [3]. There are a variety of mechanisms for linking obesity and cancer risk. Obesity increases insulin resistance, and hyperinsulinemia increases the secretion of the growth hormone, which in turn stimulates the production of carcinogens, mitogenesis, and triggers routs to oxidative stress and inflammatory process [4]. Several genes have also been studied with regard to the association between obesity and cancer; the most scientifically plausible one is FTO (fat mass and obesity-related). The association between FTO and obesity and cancer has been confirmed through the presence of single-nucleotide polymorphisms (SNPs). There are several SNPs in the FTO gene that recent studies have shown an etiologic role in incidence of breast cancer. Some of these polymorphisms include: rs9939609, rs17817449, rs8050136, rs1477196, rs6499640, rs16953002, rs11075995, and rs1121980 [5-6]. This systematic review and meta-analysis aims to 1) identify all FTO gene polymorphisms involved in the risk of breast cancer or prognosis of breast cancer, and 2) to pool the studies that report a quantitative measure of association between a FTO polymorphism and breast cancer risk and progression.

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Materials and Methods

Search Databses and Strategy

In the current study, all of the published articles related to FTO gene polymorphisms and breast cancer until 20 January, 2019 were searched in the Pubmed, embase, Science Direct, Scopus, web of science, and Cochran databases. Key words such as "fat mass and obesity associated gene" and/or "FTO", "breast cancer" and/or "breast neoplasm" and/or "polymorphism" and/or "SNP" were used in order to obtain the related articles. All articles collected in the electronic search process as well as the references used in these articles were reviewed. Irrelevant, non-English, and inappropriate articles were excluded from systematic review process based on the following inclusion and exclusion criteria.

Inclusion and exclusion criteria

Studies which have quantitatively investigated the association between FTO gene polymorphisms and breast cancer using case-control studies and odds ratio and confidence interval indicators. Studies focused on the other cases as well as those which had investigated outcomes other than breast cancer (e.g., obesity or other cancers), and studies which had investigated breast cancer in men were excluded from our review study.

Assessment of methodological rigor

At this stage, studies conducted to investigate the association between FTO gene polymorphisms and breast cancer were selected. The quality of studies was independently assessed by 2 persons (SD and MGh), and if two assessors do not agree with each other, the assessment was completed as a discussion with a third person (SAMJ). The irrelevant articles were excluded from the intended articles. The full text of the articles known as appropriate in this study was investigated. In order to assess the quality of the studies' methodology, the standardized quality assessment method for clinical trials (The EPOC Risk of Bias Tool) was used [7]. In addition, the preferred reporting items for systematic reviews and meta-analyses (PRISMA) were used in this study [8]. Figure 1 shows the selection process of the studies used in the current study and the studies excluded from this study in the order of their removal reasons. According to PRISMA guideline, we entered the intended data into the study and used pilot forms to collect the data required by these studies. All data related to participants, interventions performed, comparisons, outcomes, and studies design were (PICOS) gathered.

Results

Systematic Reviews

The Search Strategy

The following search strategy was used to search the databases:

(rs17817449 OR rs8050136 OR rs6499640 OR rs16953002 OR rs11075995 OR rs1121980 OR FTO gene polymorphism) AND (breast cancer OR Breast Tumor OR Breast Tumor, OR Tumor of Breast, Tumor of Breast OR carcinoma of Breast, OR Breast Carcinoma).

Search Result and Study selection

The search identified 534 studies that after removal of duplication, 377 studies candid for further evaluation. Abstract evaluation resulted in 168 studies for full text evaluation in which 16 studies were included in this study. Table 1 present the details of the final studies used in this analysis. Figure 5 presents the PRISMA flowchart of the studies included in this analysis.

Meta-analysis

We consider all the models of inheritance and report those that did showed association. Two polymorphisms of (rs1477196) and (rs9939609) had significant associations. No significant association was found between rs17817449 and rs11075995 polymorphisms and breast cancer.

Polymorphism rs1477196

There was an inverse association between the rs1477196 polymorphism and BC (OR 0.76 [0.64- 0.91]). There was not observable heterogeneity (I2: 0.0%,

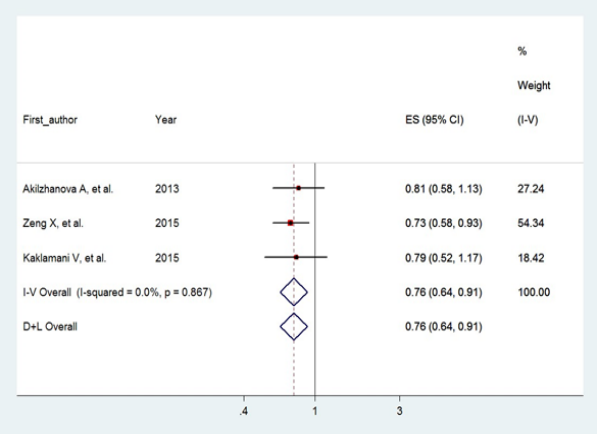

Figure 1. Forest Plot of the Association between rs1477196 Polymorphism and Breast Cancer

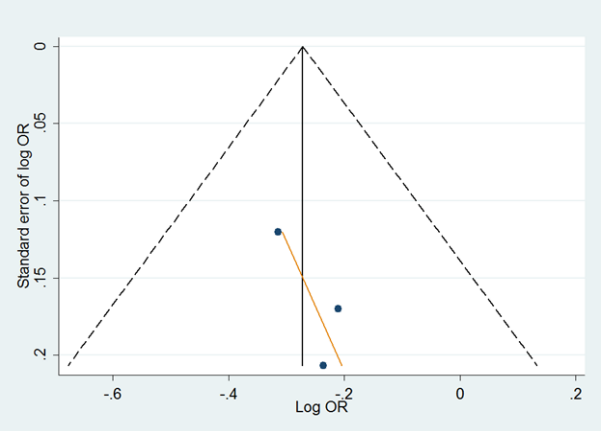

Figure 2. Funnel Plot of the Association between rs1477196 Polymorphism and Breast Cancer

Table 1. Studies that were Used to do the Meta Analysis

	Study	Country	Ethnicity	Case/control	OR	95%CI	Result
	rs9939609-rs1121980						
1	Zeng (2015)	China	East Asia	537/537	1.9	0.90-1.57	FTO gene variants (rs9939609rs1477196rs1121980) are associated with the risk of breast cancer.
2	daCunha (2013)	Brazil	European	100/148	0.86	0.60-1.25	There was no association between rs9939609 and rs1121980 polymorphisms and the risk of breast cancer.
3	Zhao (2016)	European countries	European	62328/83 817	0.94	0.92-0.95	There is a significant association between rs9939609 polymorphism and the risk of breast cancer.
4	Kusinska R (2012)	Poland	European	134/357	1.05	0.68-1.61	Rs9939609 polymorphism is not associated with the risk of breast cancer.
5	Brooks (2012)	US and Denmark	European	643/1271	1.02	0.93-1.13	Rs9939609 polymorphism is not associated with the risk of breast cancer.
6	Kaklamani (2011)	USA	Mixed	302/349	0.506	0.30- 0.88	Rs993909 polymorphism is associated with the risk of breast cancer.
7	Mojaver (2015)	Iran	Middle East	99/100	1.215	0.683- 2.161	Rs9939609 polymorphism is not associated with the risk of breast cancer.
	rs1477196						
1	Kaklamani (2011) [19]	USA	Mixed	302/349	1.447	1.13- 1.85	Rs1477196 polymorphism is strongly associated with the risk of breast cancer.
2	Zeng (2015) [14]	China	East Asia	537/537	0.54	0.34- 0.86	Rs1477196 polymorphism was associated with breast cancer only in subjects with BMI less than 24
3	Akilzhanova (2012)	Kazakhstan	European	315/604	0.96	0.78- 1.17	Rs1477196 polymorphism is not associated with the risk of breast cancer.
4	Mojaver (2015)	Iran	Middle East	99/100	0.890	0.464- 1.707	Rs1477196 polymorphism is not associated with the risk of breast cancer.
	rs11075995						
1	Zeng (2015)	China	East Asia	537/537	0.9	0.71- 1.15	Rs1477196 polymorphism is not associated with the risk of breast cancer.
2	Zhang (2014)	China	East Asia	2901/2789	1.06	0.98- 1.14	Rs11075995 polymorphism is not associated with the risk of breast cancer.
3	Garcia-Closas (2013)	USA and European countries	European	10706/76647	1.11	1.07- 1.15	An association was observed between rs1107599 polymorphism and the risk of breast cancer.
	rs17817449						
1	Long (2013)	USA	Africans	1113/930	1.32	1.09- 1.6	Rs1781744 polymorphism is associated with the risk of breast cancer.
2	Zheng (2013)	China, Korea, Japan and Thailand	East Asia	16797/18 983	0.92	0.88- 0.97	Rs1781744 polymorphism is associated with the risk of breast cancer.

P=.867), but with a small study effect (b=1.19, P=.03) in this analysis (Figure 1 and 2).

Polymorphism rs9939609

Moreover, there was not any association between the rs9939609 polymorphism and BC (OR 0.98 [0.79- 1.2]). There was not observable heterogeneity (I2: 23.1%, P=.27) and small study effect (b=-3.817, P=.303) in this analysis (Figure 3 and 4).

Discussion

FTO gene was for the first time identified in animal models as a gene affecting programmed cell death. Mice harboring mutations in this gene have fused toes and larger thymus than most other mice [9-10]. FTO gene encodes a 2-oxoglutaratedependent oxigenase that plays a role in DNA demethylation. This gene is located on human chromosome 16q12.2. Duplication of this gene region leads to mental retardation, obesity and other abnormalities [11]. FTO gene is expressed in all body tissues; however, its highest expression has been in the brain and hypothalamus [12].

Two years after the publication of the article on the association between genetic differences of FTO gene and obesity, the researchers began their research on the association between genotype differences in this gene and the risk of cancer in obese people of different races [13]. Quantitative studies have been conducted on the association between FTO gene variants and breast

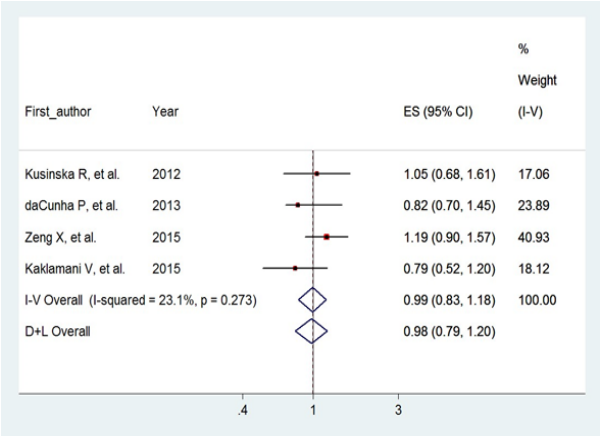

Figure 3. Forest Plot of the Association between rs9939609 Polymorphism and Breast Cancer

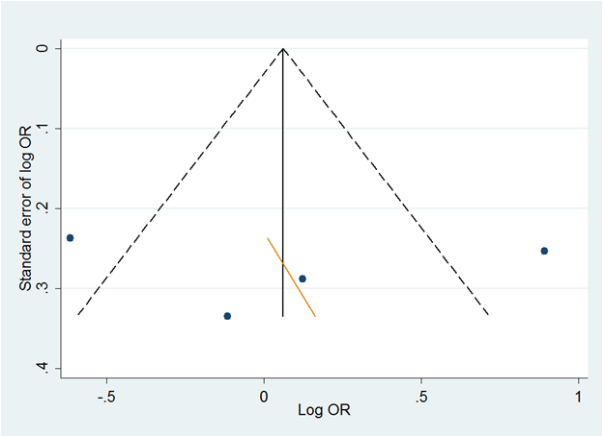

Figure 4. Funnel Plot of the Association between rs9939609 Polymorphism and Breast Cancer

cancer and various results have been obtained from these studies. The reason for part of these differences may be due to the racial differences in the study groups. For example, in a study conducted on Iranian women, Mojaver et al. concluded that there is no significant association between rs9939609 and rs1477196 polymorphisms and the risk of breast cancer [14], but in other studies, a significant association was observed between the four FTO polymorphisms (rs7206790, rs8047395, rs9939609, and rs1477196) and the risk of breast cancer [15]. In a meta-analysis conducted on the association between FTO gene rs9939609 polymorphism and breast cancer, it was found that rs9939609 polymorphism in FTO gene is associated with the risk of breast cancer in Asian race [16].

Additionally, a case-control study conducted on different races showed that the risk of breast cancer for rs1477196 polymorphism in people with homozygous dominant alleles (AA) is 2.38 times higher than individuals with genotypes GG [15]. This is while, no association was observed between this polymorphism and the risk of cancer in other studies conducted on a particular race [15-17]. The major cause of these differences may be due to racial differences in different individuals. The frequency of FTO gene polymorphisms is very different in different races. For example, the frequency of rs9930506 polymorphism in Chinese individuals was reported to be less than 0.1 [18], while the frequency of this polymorphism is approximately 0.4 in white societies.

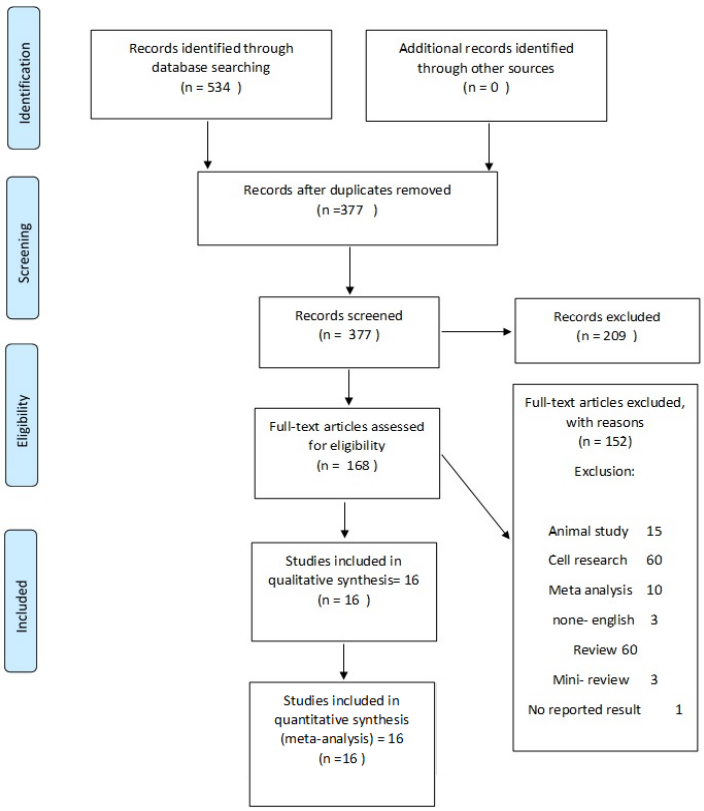

Figure 5. The Search Flow Chart

In addition, cultural and environmental factors may also affect the role of race in the association between FTO gene and breast cancer. For example, the rate of FTO gene expression is associated with breast cancer, and recent studies have shown that dietary composition also affects the rate of FTO gene expression [3]. Differences in dietary intake in different races may justify part of difference in the results reported in previous studies on the association between FTO gene and breast cancer.

In conclusion, generally, the results of studies in this field showed that there is an association between FTO gene, obesity and breast cancer. There have been very few studies conducted in this regard. More human studies are required to assess the interface between existing mechanisms of the effects of these genes on breast cancer.

Acknowledgments

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