

The Evaluation of p53 Polymorphism at Codon 72 and Association With Breast Cancer in Iran: A Systematic Review and Meta-analysis

ORIGINAL
ARTICLE

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Background: Breast cancer is the most common cancer among women in Iran and the world. Multiple environmental factors and genetic variations such as genetic polymorphisms are of its main causes. p53 gene plays an important role in conserving and sustaining the genome as a tumor suppressing gene. Change and polymorphism at codon 72 of p53 gene are correlated with increased risk of lung, mouth, endometrial, prostate, and colorectal cancers, and could be considered an indicator of susceptibility to breast cancer.

Methods: Twelve studies (1,190 cases and 1,145 control studies with evaluation of three types of Arg/Arg, Arg/Pro, and Pro/Pro genotypes) have been conducted using keywords, such as polymorphism at codon 72, gene p53 polymorphisms, and the relation between polymorphisms and breast cancer, from databases in Iran, including Magiran, Medlib, Sid, and Iranmedex, as well as Latin databases such as PubMed, Google Scholar, Science Direct, and Scopus.

Results: The OR for Arg/Arg is 1.58 (95% CI: 2.45 to 1.01), the OR for Arg/Pro is 0.75 (95% CI: 1.10 to 0.51), and the OR for Pro/Pro is 0.62 (95% CI: 0.93 to 0.42). p53 gene polymorphism at codon 72 is statistically significant in Arg/Arg and Pro/Pro genotypes.

Conclusions: Arg/Arg genotype can be considered as a risk factor for breast cancer, and Pro/Pro genotype can be accounted for as a protective factor against breast cancer.

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Key Words: Breast neoplasms, Polymorphism, p53, Codon 72

INTRODUCTION

Breast cancer is among cancers with high prevalence and is the second most common cancer in women around the world.^{1,2} Thirty percent of all cancers and 15% of cancer-caused deaths among women are due to this cancer.³ According to the report of World Health Organization in February 2009, the annual breast cancer death rate is 519 thousand people worldwide.⁴ Breast cancer still has the first place in Iran regarding the population of the contracted.⁵ A total number of 40 thousand people are diagnosed with breast cancer in Iran and more than seven

thousand patients are added to this number each year.⁶

In general, risk factors for breast cancer are unknown, but factors, such as family history, genetic background, age of menarche and menopause, age of first childbirth, hormone use, alcohol consumption, and previous history of cancer, can be considered.⁷ p53 gene polymorphism is one of the factors regarded by researchers as the cause of breast cancer. This gene with the length of 20 kilo-base pair is in 17p13.1 (short arm of chromosome 17) which contains 11 exons and its translated mRNA codes a protein with molecular weight of 53 kDa which contains 393 amino acids.⁸ Its normal function is to protect

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genome against damages, leading to genome repair or apoptosis and eliminating carcinogenic cells in this way.⁹ p53 gene inactivity due to mutation leads to protein breakdown or allelic loss. This gene has an important role in regulating cells' fate in response to various stresses, such as radiation, carcinogens, toxic drugs, hypoxia, nucleotide deficiency, oncogenic activity, defragmenting microtubules, or loss of normal cellular connection.¹⁰ In addition, codon 72 of p53 exon 4 has a common polymorphism in which the displacement effect of C to G leads to creation of two arginine or proline proteins. Activities of these two proteins are different, and they affect genes' function.¹¹ This polymorphism codes three genotypes of homozygous arginine (Arg/Arg), heterozygous (Arg/Pro), and homozygous proline (Pro/Pro).¹² A lot of studies have been conducted to evaluate the role that these three genotypes play in breast cancer worldwide and have reported different results in this field. For example, the studies of Khadang et al.,¹³ Kazemi et al.,¹⁴ and Agorastos et al.¹⁵ in Greece and Vijayaraman et al.¹⁶ in southern part of Maduria found no significant relationship between polymorphism of this codon in p53 gene and breast cancer. In contrast, the studies of Sheikhpour and Zahir¹⁷ and Golmohammadi and Namazi¹⁸ showed a significant relationship. Moreover, a great number of other studies from around the world also showed a significant relationship between breast cancer and some genotypes of this polymorphism^{19,21} and even reported different results in the concluded meta-analysis in terms of the effect of different genotypes on breast cancer. The share of Iranian researches conducted on this subject matter was not more than two articles in these meta-analyses.^{22,23} These two articles were reasons enough for carrying out a structured review of studies conducted in this field in Iran to provide more reliable statistics of this category.

MATERIALS AND METHODS

The present study is to evaluate the rate of polymorphism of p53 gene codon 72 and its relationship to breast cancer risk in women. This has been carried out by collecting, documenting, employing case control studies that have been done in this area, and meta-analyzing the existing findings. Articles published in national and international journals in databases, such as Ramedex, SID, Magiran, Irandoc, Science Direct, as well as articles presented at conferences or used to find surveys conducted in the country are of other sources on which this study has been constructed. Searching for relevant researches was performed through identifying Persian keywords with all of their possible combinations. Moreover, Persian keywords, such as poly-

morphism at codon 72, polymorphism of the gene p53, the relationship of polymorphisms and breast cancer, as well as English keywords including p53 polymorphism at codon 72, p53 polymorphism, and breast cancer, were used to increase the sensitivity of the present study. Finally, abstracts of researches were studied by the researchers based on inclusion and exclusion criteria after finding out the articles being concerned with codon 72 polymorphism and p53 gene polymorphism and selection of articles that had full connection with the research subject. Then, unrelated articles were excluded, and articles related to research were determined in order to download their full text and carry out extraction. The data of the prepared studies were extracted after entering selected articles into the study and approving the quality control using pre-prepared checklist. The prepared checklist was used to extract data using factors such as: article's title, the first author, the rank of the article, the research date, the total sampling size in case and control groups, and the ratio of each of the three Arg/Arg, Arg/Pro, and Pro/Pro genotypes in both case and control groups. All data were extracted from the studies and were entered into the mentioned form.

Fifty-four articles were examined in this process. After that, 25 articles which included the basic information were fully studied. Then, 17 articles were removed due to being about the effect of this gene on other cancers and being conducted in other countries. Finally, 12 articles that were conducted on Iranian women between 2007 and 2014 were included into the analysis process.

In this step, all cross-sectional studies in the field of gene p53 polymorphism at codon 72 and its relation with breast cancer risk in Iran, which all were cross-sectional studies, were collected and given that the prevalence of polymorphism had binomial distribution in both groups. The variance of each study was calculated through binomial distribution variance. Weight given to each study was inversely proportional to the variance, and I^2 index was used to evaluate heterogeneity between data. Data analysis was done using Stata ver. 11 software (Stata Corp, College Station, TX, USA). P lower than 0.05 was considered to be significant in the case of heterogeneity test.

RESULTS

In this research, the highest OR of developing breast cancer was detected in people with Arg/Arg genotype as a research of Faghani et al.²⁴ demonstrated and the OR was related to the study of Ghasemifrouzabadi et al.²⁵ Of these 12 studies, 7 studies reported that the OR of developing breast cancer in Arg/Arg genotype is significant. Six studies^{4,17,18,26,28} reported Arg/Arg

genotype as a disposing factor for breast cancer and Ghasemifirouzabadi et al.²⁵ reported this genotype as a protective factor against cancer in women. Other inquiries have not discovered any significant relationship between Arg/Arg genotype and breast cancer risk (Table 1).^{13,14,17-31}

However, it was determined after a meta-analysis that the OR of developing breast cancer in Iranian women with Arg/Arg genotype is 1.58 (95% CI: 1.01 to 2.45) (Fig. 1).

Five studies were statistically significant in evaluation of OR of developing breast cancer in patients with Arg/Pro genotype. Only the study of Boroujeni et al.³¹ reported the role of Arg/Pro genotype as a risk factor for cancer, and the other four^{17,24,26,28} recorded this genotype as a protective factor against breast cancer. However, other studies did not account for a significant relationship between Arg/Arg genotype and breast cancer risk. It

was decided after the meta-analysis that the OR of developing breast cancer in people with Arg/Pro genotype is 0.75 (95% CI: 0.51 to 1.10) (Fig. 2).

It was conformed from the evaluation of concluded studies in the field of p53 gene codon 72 polymorphism, its relationship with breast cancer risk in Iran, and the role of Pro/Pro genotype in breast cancer risk that 4 studies out of these 12 studies were statistically meaningful: only the study of Kazemi et al.¹⁴ reported the existence of Pro/Pro genotype in individuals as a factor that stimulates breast cancer, and other three studies noted that this genotype is a securing agent against breast cancer. No compelling relationship was established between Pro/Pro genotype and breast cancer risk in other studies. After carrying out the meta-analysis and the evaluation of each study in Iran, it was determined that the OR of developing breast cancer in people

Table 1. Reviewed articles on p53 gene codon 72 polymorphism and its association with breast cancer risk in Iran

First author	Year	Location study	Case (n)	Control (n)	OR (95% CI)		
					Pro/Pro	Arg/Pro	Arg/Arg
Faghani ²⁴	2007	Esfahan	51	51	0.490 (0.043-5.580)	0.119 (0.043-0.327)	8.286 (3.137-21.883)
Yasebi ²⁹	2007	Chaharmahal	85	50	0.384 (0.115-1.282)	1.755 (0.830-3.714)	0.792 (0.342-1.832)
Khadang ¹³	2007	Entire country	221	205	0.623 (0.370-1.049)	1.244 (0.849-1.821)	1.043 (0.703-1.545)
Faghani ²⁶	2008	Esfahan	96	96	0.365 (0.144-0.927)	0.331 (0.176-0.621)	4.233 (2.311-7.754)
Kazemi ¹⁴	2009	Northern Iran	42	57	20.47 (1.120-374.5)	0.667 (0.265-1.679)	0.625 (0.214-1.829)
Doosti ²⁷	2011	Entire country	135	140	0.572 (0.275-1.187)	0.762 (0.473-1.227)	1.810 (1.083-3.025)
Hossein Pour Feizi ²⁸	2012	Eastern Azerbaijan	126	99	1.095 (0.565-2.119)	0.526 (0.307-0.901)	1.840 (1.057-3.203)
Ghasemifirouzabadi ²⁵	2013	Yazd	90	83	1.476 (0.785-2.778)	1.243 (0.683-2.262)	0.369 (0.162-0.840)
Boroujeni ³¹	2013	Central Iran	135	150	0.286 (0.112-0.731)	1.894 (1.135-3.163)	0.792 (0.450-1.392)
Golmohammadi ¹⁸	2013	Sabzevar	80	80	0.121 (0.027-0.551)	0.899 (0.474-1.705)	2.464 (1.196-5.078)
Behfarjam ³⁰	2013	Mahabad	25	30	0.565 (0.095-3.378)	0.973 (0.334-2.838)	1.313 (0.424-4.063)
Sheikhpour ¹⁷	2014	Yazd	104	104	0.728 (0.384-1.381)	0.393 (0.222-0.695)	3.587 (1.953-6.586)

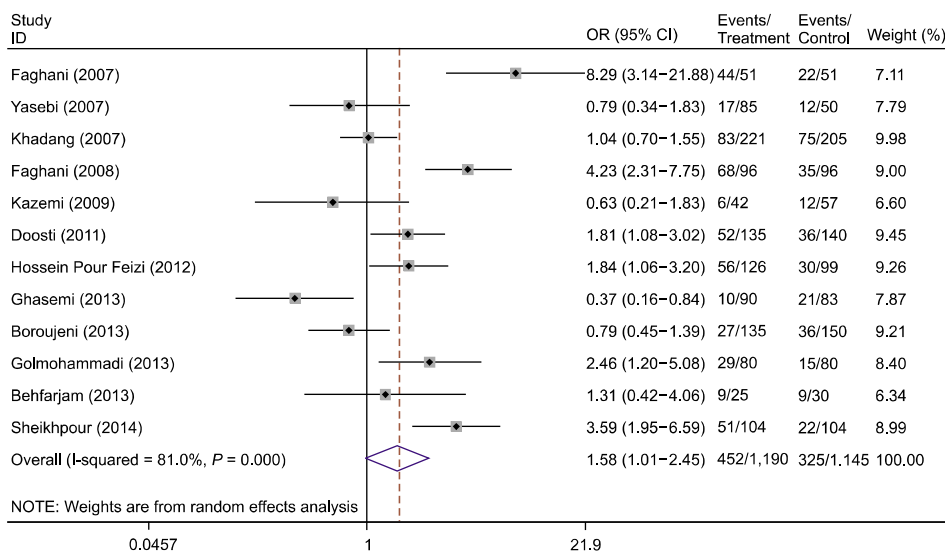


Figure 1. The OR of developing breast cancer in patients with Arg/Arg genotype in the Iran.

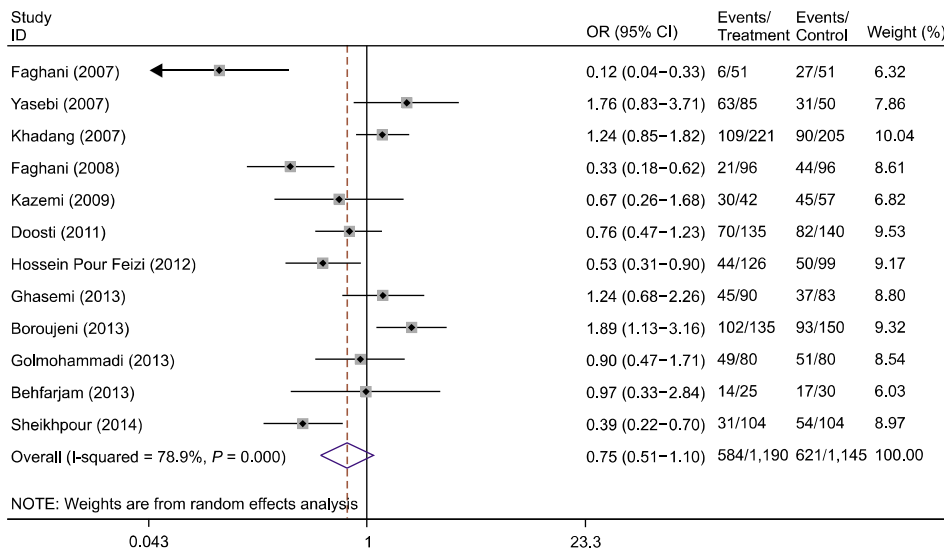


Figure 2. The OR of developing breast cancer in patients with Arg/Arg genotype in the Iran.

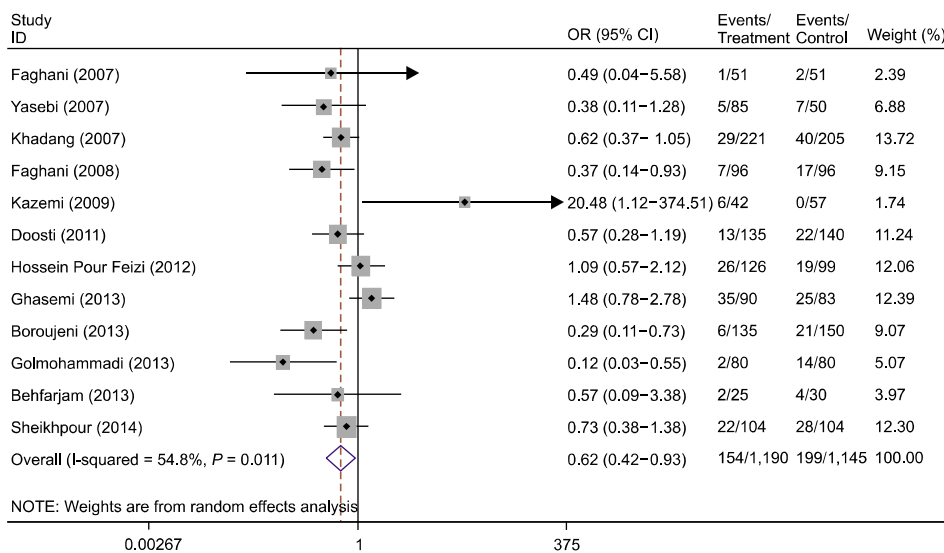


Figure 3. The OR of developing breast cancer in patients with Pro/Pro genotype in the Iran.

with Pro/Pro genotype is 0.62 (95% CI: 0.42 to 0.93) (Fig. 3).

Egger test was used to evaluate publication bias to find out whether this bias has affected the results, and the diagram 4 shows that publication bias has not affected the obtained results (Fig. 4).

DISCUSSION

Numerous studies have been carried out in the field of p53 codon 72 polymorphism and its correspondence with breast cancer risk throughout the world. Some of these studies believe that changes in a particular p53 gene codon 72 genotype predispose females to breast cancer, and other studies have considered the same change as a preventing factor. Meta-analyses

have been done within this domain in different races, among which there are only two Iranian studies. However, there is no analysis along with statistical weighting for concluded studies in Iran in order to have a comprehensive perception on the role of this polymorphism in risk of breast cancer in Iranian women. The OR of breast cancer for three Arg/Arg, Arg/Pro, and Pro/Pro genotypes were calculated in the present research. OR of developing breast cancer in Iranian women with genotype Arg/Arg is 1.58 (95% CI: 1.01 to 2.45). This can be statistically considered as a predisposing factor for developing breast cancer in Iranian women because OR does not contain number 1. This result is in tandem with the studies of Doosti et al.²⁷ and Hossein Pour Feizi et al.²⁸ Meta-analyses of Gonçalves et al.²³ and Buyru et al.³² concluded in a study conducted in Turkey that the risk of

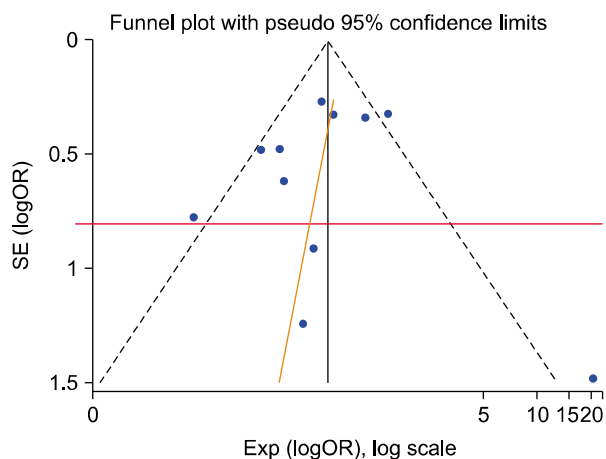


Figure 4. Diagram of publication bias for p53 gene codon 72 polymorphism and its association with breast cancer risk in Iran.

breast cancer is higher in patients with Arg/Arg genotype.

The OR of developing breast cancer in patients with Arg/Pro genotype was 0.75 (95% CI: 0.51 to 1.10). Arg/Pro genotype has no effect on the risk of breast cancer which is in line with the results of many domestic studies, such as Doosti et al.²⁷ and foreign researches of Hou et al.³³

After examining the results of the aforementioned studies, it was determined that the OR of developing breast cancer in people with Pro/Pro genotype is 0.62 (95% CI: 0.42 to 0.93). This was statically important because the OR does not contain 1, in a way that Pro/Pro genotype can be regarded as a protective factor against breast cancer in Iranian women. This accords with the study results of Sheikhpour and Zahir¹⁷ and Faghani et al.,²⁶ and Alawadi et al.³⁴ who concluded that the risk of breast cancer is lower among Arab women with Pro/Pro genotype.

At the end, it should be noted that due to the scarcity of studies in this field in Iran, it is required for direct studies about p53 gene codon 72 polymorphism and its relationship to breast cancer risk in Iran so that the obtained results can be used clearly and more importantly.

CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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