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RESEARCH PAPER

Quantitative analysis of p53 substitution mutation and breast cancer; An informative study in Iranian population

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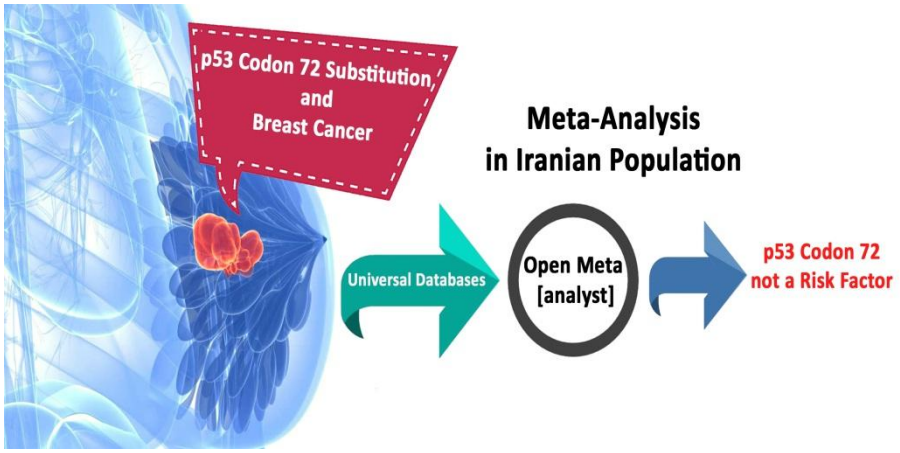
Highlights

- Genetic variations in tumor suppressor genes such as p53 protein could impact breast cancer.
- One of main gene variations is p53 codon 72 which could alter the risk of breast tumors.
- The codon 73 in p53 is not a risk factor for breast cancer in Iranian population.

Graphical Abstract



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Abstract

Genetic factors including genetic variations in important genes may influence breast cancer susceptibility. One of important gene variations is p53 codon 72 which might impact risk of breast cancer. There are three case-control genetic association studies regard to the relation of this polymorphism with breast cancer risk in Iranian females, but the outcomes are indecisive. So, a meta-analysis was made in Iranian population in this regard. The eligible studies were found using search in appropriate databases. So, the extracted information from comprised studies was examined by Open Meta analyst program. The analyzed data displayed that there is no substantial correlation of p53 codon 72 substitution with risk of breast cancer in CC vs. GG (OR= 0.844, 95%CI= 0.244-2.916, p= 0.789) and GC vs. GG (OR= 1.215, 95%CI= 0.880-1.676, p= 0.237) models in Iran. Regarding to the outcomes, the aforementioned polymorphism is not a molecular risk factor for breast cancer in Iranian population.

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Introduction

Breast cancer is one of malignant cancer among woman worldwide which is involved epithelial cells lining the lobules or ducts of the breast (1). The etiology of breast cancer remains vague, but some genetic and environmental factors such as hormones, cigarette smoking, and alcohol consumption can effect on this disease (2). One the genetic factors involved in breast cancer is the p53 protein as a tumor suppressor (3).

The loci-coding p53 tumor suppressor protein has a key role in cellular reactions to DNA damage. Activation of p53 leads to either development arrest in the phase of G1 of the cell cycle or program cell death (4). The gene, as mentioned earlier, contains many mutations and variations (5). Gene mutations in the p53 are associated with >50% of cancers in humans, significantly 90% of them impact interactions of p53-DNA due to loss of a partial or complete transactivation action (6). The p53 gene with a 17p13 chromosomal location is one of the most often modified genes in most kinds of cancers in humans (7). The tumor suppressor p53 is commonly altered in numerous kinds of cancers. A common polymorphism occurred at exon 4 of p53 in the codon 72 location (8). The codon 72 polymorphism has two alleles at codon 72 with a transition of CGC to CCC, resulting in a substitution of arginine (Arg) to proline (Pro) residues (Arg72Pro) (9). Codon 72 genetic polymorphism reportedly correlated with breast cancer (10).

Some experimental reports have been done to illustrate the association of the codon 72 substitution in p53 and the risk of breast cancer in the Iranian population. Nevertheless, the outcomes are not consistent. The documents might be analyzed by performing a meta-analysis, and the sample size enlarged to a suitable amount. In the current study, a quantitative synthesis meta-analysis has been performed to investigate the correlation of the codon 72 variation in p53 protein with breast cancer risk in Iranian females (11).

Materials and Methods

Publication search

The databases, such as Google Scholar, PubMed, Scopus, ISI, Sid, Magiran, and Iran medex, were searched by utilizing the keywords “codon 72”, “variation”, “polymorphism”, “p53”, “breast cancer”, “Iran”. All the case-control investigations, including accessible frequencies of the genotype of Arg72Pro were chosen.

The criteria for study selection

The inclusion standards were: 1) case-control design; 2) assessing the correlation of the codon 72 in p53 protein with breast cancer risk; 3) providing adequate data to compute the odds ratio (OR) and % corresponding confidence interval (CI). PRISMA rules were used for paper selection.

Statistical analysis

The ORs with 95% CIs for the association of p53 codon 72substitution with breast cancer risk were measured for each included paper. For the variation, the breast cancer risk was estimated for the GC and CC vs. GG wild-type so, the breast cancer risk for CC vs. GG and GC vs. GG co-dominant genetic models. Heterogeneity among studies was measured using the Chi-square-based Q test. The heterogeneities among studies were considered substantial when I^2 >50%. The model of Mantel-Haenszel fixed-effects and DerSimonian random-effects model were employed to pool data from each included study (12). The fixed effects was used when the homogeneity was substantial; else, the random effect model is more suitable. All analyses were done in the Meta Analyst software. All p values in this study were two-tailed (13).

Results

Flow diagrams for paper selection are presented in Figure 1. Three case-control reports investigating the correlation of codon 72 substitution in p53 molecule and breast tumor risk are recognized, comprising 398 breast tumor subjects and 415 healthy subjects in Iran (14). The data extracted from these three studies were employed in a quantitative synthesis (Table 1). The genotypes distribution in the control subjects of Khadang et al. (2007) was consistent with Hardy-Weinberg equilibrium (15).

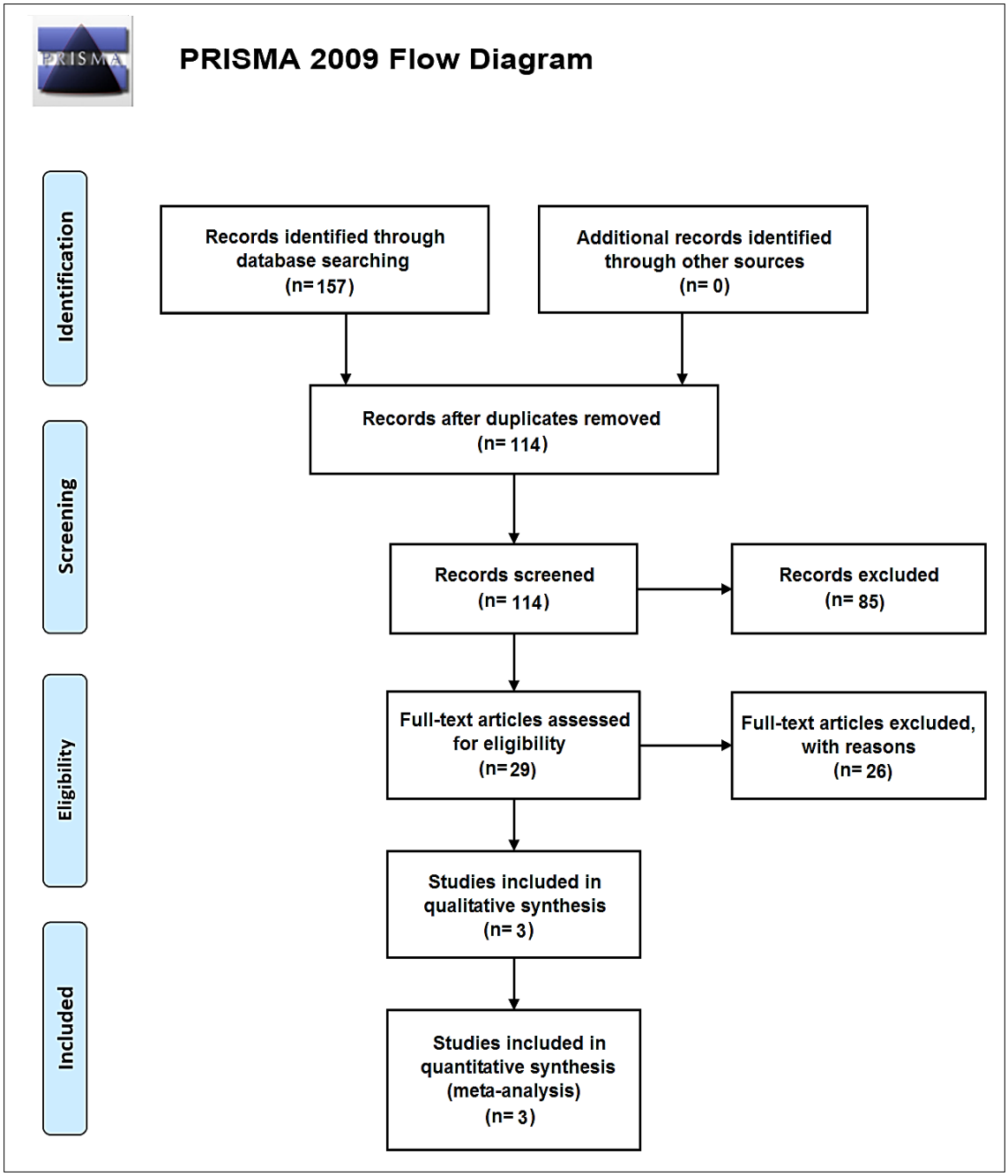

Figure 1. PRISMA diagram. A total of three papers were selected in this study.

Table 1. Features of p53 codon 72 variations in three included papers in meta-analysis.

Genotype frequencies						HWE P[a]	Genotyping method	Reference
Control			Case					
GG Arg/Arg	GC Arg/Pro	CC Pro/Pro	GG Arg/Arg	GC Arg/Pro	CC Pro/Pro			
75	90	40	83	109	29	0.171	PCR-RFLP	Khadang et al., 2007 (14)
12	48	0	6	30	6	0.000	AS-PCR	Kazemi et al., 2009 (15)
36	93	21	27	102	6	0.002	AS-PCR	Hu et al., 2013 (16)

PCR-RFLP: Restriction fragment length polymorphism-polymerase chain reaction; AS-PCR: allele-specific polymerase chain reaction.

The association outcomes of the codon 72 substitution in p53 and breast tumor and the heterogeneity assessment are detailed in Tables 2 and 3, respectively. The obtained data revealed that there is no statistically significant association between codon 72 in p53 and breast cancer in Iranian population in CC vs. GG (OR= 0.844, 95%CI= 0.244-2.916, p= 0.789) and GC vs. GG (OR= 1.215, 95%CI= 0.880-1.676, p= 0.237) models. Also, the results showed true heterogeneities in CC vs. GG ($P_{heterogeneity=}$ 0.037, I^2= 70%) while there is no significant heterogeneity in GC vs. GG ($P_{heterogeneity=}$ 0.725, I^2= 0%) models. The test of Egger illustrated no publication bias in the analysis (Table 3).

Table 2. Outcomes of meta-analysis.

Genetic model	Analysis model	OR (95%CI)	P-value
CC *vs*. GG	Random effect	0.844 (0.244-2.916)	0.789
	Fixed effect	0.716 (0.448-1.143)	0.162
GC *vs*. GG	Random effect	1.214 (0.879-1.677)	0.238
	Fixed effect	1.215 (0.880-1.676)	0.237

Table 3. Results of heterogeneity and publication bias.

Genetic model	tau²	Q(df=2)	PH	I²	P-Egger
CC *vs*. GG	0.746	6.597	0.037	70%	0.529
	-	6.806	0.033	71%	
GC *vs*. GG	0.000	0.644	0.725	0%	0.712
	-	0.644	0.725	0%	

Discussion

Because of the key roles of p53 protein in numerous cellular actions, such as regulation of cell cycle, apoptosis, and repair of DNA, p53 mutations and polymorphisms may probably be correlated with breast cancer risk. Although the possible molecular mechanism involved in breast cancer remains comparatively indefinite single nucleotide polymorphisms or, an abbreviation, SNPs, can employ as a helpful device to examine multifactorial disorders vulnerability (16). Several former reports have established a substantial correlation of the common codon 72 substitution in p53 and risk of breast tumor in the Iranian population; some others have presented no significant correlation. To discover the relation, in the current project, a quantitative synthesis meta-analysis was done to study the correlation between the mentioned p53 variation and risk of breast tumor (17). Overall, 398 breast cancer subjects and 415 healthy subjects from 3 reports were involved in the last meta-analysis to develop a more exact assessment of this correlation's absence or presence (18).

The resulted data revealed no significant associations between codon 72 in p53 protein and risk of breast tumor in the Iranian population in models of CC vs. GG and GC vs. GG. Also, the true heterogeneities in CC vs. GG was found and whereas there is no significant heterogeneity in GC vs. GG models (19). The different results in different studies may arise from geographical and environmental differences (20). Khadang et al. (14) were used PCR-RFLP for SNP genotyping, while Kazemi et al. (15) and Hu et al. (16) were used AS-PCR for SNP genotyping.

The p53 tumor protein, too recognized as p53, phosphoprotein p53, TRP53, and antigen NY-CO-13, is every protein isoform encoded by similar genes in a variety of organisms, such as humans (TP53) and mice (Trp53) (21). This molecule is essential in organisms because it prevents tumor formation, therefore, acts as a tumor suppressor (22). Since the p53 describes as "the genome guardian" because of its function in constancy protection by interdiction genome mutationhis molecule has numerous anti-cancer mechanisms, and it has a central role in the stability of the genome, apoptosis, and inhibition of angiogenesis (23). For playing an anti-cancer role, p53 acts via some mechanisms such as 1) It could stimulate proteins involved in DNA repair when

DNA is damaged (24). Therefore, it might be a critical factor in the aging process. 2) It could play central role at the G1/S step of the cell cycle to recognize DNA damage (25). 3) It could promote apoptosis when DNA damage occurs in the cell, and 4) It is necessary for the response of senescence to small telomeres (26).

Some possible mechanisms could explain the role of codon 72 variation in p53 in carcinogenesis. Overall, non-synonymous single nucleotide polymorphisms (nsSNPs) could affect RNA structure and protein function protein (27). Therefore, codon 72 polymorphism could affect these parameters of p53 protein (28). In silico analysis is a helpful tool for evaluating the damaging effects of SNPs (29). Therefore, it is suggested further in silico studies focused on this issue.

Conclusion

The p53 codon 72 substitution could not be considered as a risk factor for breast cancer risk. However, the given outcomes could be a preliminary study, and more molecular evidence is needed for these outcomes. Moreover, some limitations should be known. Firstly, the results found in the current study are established on unadjusted assessments. A more precise analysis can be directed if more completely separate data were accessible to be adjusted with other varieties, such as premenopause, postmenopause, family history, smoking and drinking status, basal metabolic index, etc environmental factors.

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