



## Association of p53 codon 72 Arg>Pro polymorphism and risk of cancer in Iranian population: A systematic review and meta-analysis

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### Abstract

**Background:** Different studies have investigated the association between p53 codon 72 Arg>Pro polymorphism and cancer risk. Because of the lack of consensus of the results in individual studies, we conducted this meta-analysis by pooling all currently available case-control studies to estimate the effect of p53 codon 72 Arg/Pro polymorphism on cancer susceptibility in Iranian population.

**Methods:** A comprehensive search was undertaken and primary data from all peer-reviewed journals indexed in PubMed, Google Scholar, Scopus, Magiran, Scientific Information Databank (SID), Iran Medex, and CAB abstract electronic were used to conduct this meta-analysis. We considered some exclusion and inclusion criteria to select the articles. Statistical heterogeneity was explored using the I-square. Publication bias was assessed graphically and statistically by Begg's funnel plot and Egger test. All statistical analyses were performed using StatsDirect software and a two-tailed test. P-value less than 0.05 was considered statistically significant for any test.

**Results:** Our dataset, which included 35 case-control studies, consisted of 2426 cancer cases and 2928 controls. Pooled OR and 95%CI indicated that codon 72 Arg>Pro polymorphism was not associated with odds of developing cancer among Iranian population in the dominant model (Pro/Pro+Arg/Pro vs. Arg/Arg: OR= 0.96, 95%CI= 0.74 to 1.24  $\chi^2= 0.06$ ,  $p= 0.8$ ). Moreover, no significant association was detected in variant allele (Pro vs Arg: OR= 1.075, 95%CI= 0.91 to 1.25), homozygous (Pro/Pro vs Arg/Arg: OR=0.911 95%CI= 0.66 to 1.25), and heterozygous (Arg/Pro vs Arg/Arg: OR= 0.84, 95%CI= 0.7 to 1).

**Conclusion:** Our study revealed that p53 codon 72 Arg>Pro polymorphism was not associated with overall cancer odds in Iranian population.

**Keywords:** Meta-analysis, Cancer, p53, Iran

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### Introduction

About 12.7 million cancer cases and 7.6 million cancer deaths were estimated to occur in 2008 worldwide. Cancer is one of the most common causes of death worldwide (1). Cancer incidence rate depends on multi-environmental factors including geographical region, habitats, life style, and genomic variation (2). TP53 is a tumor suppressor gene, containing 11 exons and 10 introns, located on chromosome 17p13 (3). TP53 gene encodes p53 protein that binds to promoters and introns of genes and involves many proteins including components of the basal transcriptional apparatus, histone acetyl transferases, and other transcriptional cofactors, which are essential for transcrip-

tional initiation (4-6). This protein function results in gene transcription, DNA repair, apoptosis, senescence, or temporary cell cycle arrest under a variety of circumstances and mechanisms including genotoxic stresses, oncogenic signaling, and hypoxia (5, 7).

The lack of proper function of p53 is associated with many types of cancer including cervical, prostate, gastric, breast, endometrial, hepatocellular, and ovarian carcinomas (8-15). Single nucleotide polymorphisms (SNPs) are the most common form of tumor-associated mutations in p53. Among 10 polymorphisms that are described in this gene, G to C (Arg/Pro) transversion in Codon 72 in Exon

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#### ↑What is "already known" in this topic:

Meta-analysis is a useful statistical tool for combining the results from individual studies to provide results that are more trustworthy.

#### →What this article adds:

Codon 72 Arg>Pro polymorphism was not associated with odds of developing cancer among Iranian population.

4 is a common polymorphism and is associated with an increased risk of various types of cancer (16). The p53 P72 allele is weaker than the R72 allele in inducing apoptosis and suppressing cellular transformation, but appears to be better at initiating senescence and cell cycle arrest (17, 18). Jiang et al. performed a meta-analysis by pooling 17 publications to evaluate the possible effect of the p53 Codon 72 Arg/Pro polymorphism on oral cancer risk. They found no significant association between p53 Codon 72 Arg/Pro polymorphism and risk of oral cancer (19). Wang et al. performed a meta-analysis by pooling 14 publications and suggested that the p53 Codon 72 Arg/Pro polymorphism is a risk factor for lung cancer in the Asian population (20). Zhou et al. performed a meta-analysis by pooling 12 publications and suggested that the p53 Codon 72 polymorphism may be associated with gastric cancer among Asians, and they further indicated that difference in genotype distribution may be associated with the location, stage, and histological differentiation of gastric cancer (21). Also, Irshad et al. performed a meta-analysis by pooling 5 publications, and they found that the Codon 72 Arg>Pro polymorphism of the p53 gene might not contribute to cancer susceptibility in the Saudi population (22). As discussed earlier, previous case-control studies have investigated the association between mentioned polymorphism and cancer risk in the Iranian population. Due to the small sample size and low statistical power in each of the performed studies, the results were not reliable enough to determine the effect of this polymorphism on cancer susceptibility. Meta-analysis is a useful statistical tool for combining the results from individual studies to provide more trustworthy results (23). To date, no meta-analysis has been conducted on the Iranian population to evaluate this association. Therefore, we conducted this meta-analysis to pool all the published studies and determine the association between p53 Codon 72 G>C polymorphism and cancer risk.

## Methods

### Search Strategy for Identification of Studies

We followed "PRISMA" 2012 checklist criteria for meta-analysis. To cover overall publications, we used the following keywords: "p53 gene polymorphism", "p53 gene mutation", "p53 gene variation", "p53 codon 72 Arg>Pro", "Carcinoma" and "cancer risk", and "in Iranian population". The full texts of all relevant studies were analyzed carefully to determine whether data on the topic and abstract of interest were intact. Furthermore, the reference lists of the relevant articles and systematic reviews were investigated to ensure that no data were missed. In the selected case-control studies, blood and tissue samples of patients were collected from clinical hospitals and laboratories, and control samples were randomly selected from those who referred to clinical centers, who had no previous history of cancer and no signs and symptoms of malignancy.

### Inclusion criteria

The following criteria were used to select the studies: (1) a case-control design; (2) assessment of the p53 Codon

72 Arg>Pro and cancer risk in Iranian population; (3) recruiting histologically and pathologically confirmed cancer patients and healthy controls; (4) adequate genotyping data so that odds ratios (24) with 95% confidence intervals (CIs) could be calculated; (5) the selected studies had to be conducted on human samples; and (6) inclusion of genotype frequency of cases and controls.

### Exclusion criteria

Exclusion criteria were as follow: (1) not enough information on the distribution of p53 Codon 72 polymorphism; (2) case-only studies; (3) duplicated publications; (4) the studies that used cell line and animal subjects; (5) genotype frequency missing; (6) studies that investigated the levels of p53 mRNA expression; and (7) review articles.

### Information sources

The retrieved studies were searched through the PubMed, Google Scholar, Scopus, Magiran, Scientific Information Databank (SID), Iran Medex, and CAB abstract electronic databases. Publications in English and Persian languages from 2006 to December 2016 were included in this manuscript.

### Extracted Information

Two researchers independently extracted the crude data according to the inclusion and exclusion criteria listed above to prove the validity of the retrieved information. The prepared data included the first author's name, date of publication, type of cancer, ethnicity, number of cases and controls, and genotype frequencies. Disputes were settled by referring to a third researcher.

### Statistical analysis

The association between p53 Codon 72 Arg>Pro polymorphism and cancer risk was obtained by pooling odds ratio (OR) and 95% confidence intervals (CI). In the present study, estimation of the pooled effect was based on the weighted average from the results of the individual studies. Weighted average for each study was calculated based on sample size and variance of samples.

The random-effects (DerSimonian and Laird method) and fixed effect models (Mantel and Haenszel method) were applied.  $I^2$  statistics and Cochran's Q statistic ( $p < 0.10$ ) were used to check out heterogeneity assumption ( $I^2$  static is the percentage of the observed total variation across studies that are due to heterogeneity rather than chance). A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. Q is the weighted of squares on a standardized scale, which is reported with a p-value, with low p-values indicating the presence of heterogeneity. If  $p < 0.05$ , the results were pooled by the random-effects model, otherwise, fixed effect model was used.

To evaluate the publication bias among the included studies, Begg's funnel plot and Egger's linear regression test were performed. The Hardy-Weinberg equilibrium was calculated in the control groups using a goodness of fit test for each study. All the statistical analyses were

performed using Stats Direct software and a two-tailed test. P-value less than 0.05 was considered statistically significant for any test.

## Results

### Characteristics of publications and meta-analysis databases

In this study, 157 relevant articles were recovered by literature search. However, considering the inclusion and exclusion criteria, 67 articles were excluded because they were not relevant; moreover, 58 articles were excluded for being duplicates, not being performed on human subjects, and being review articles. After careful screening, 32 eli-

gible case-control studies on the association between p53 Codon 72 Arg>Pro polymorphism and cancer risk in the Iranian population (Fig. 1) were selected. Information including authors, date of publication, cancer type, distribution of genotypes (cases and controls), and the Hardy-Weinberg equilibrium are presented in Table 1.

### Evaluation of heterogeneity

To analyze heterogeneity among the studies, Q test,  $I^2$  statistics, and heterogeneity were noticed in all the 5 genetic models. The random effects model was used to calculate the odds ratio and 95% confidence interval (Table 2).

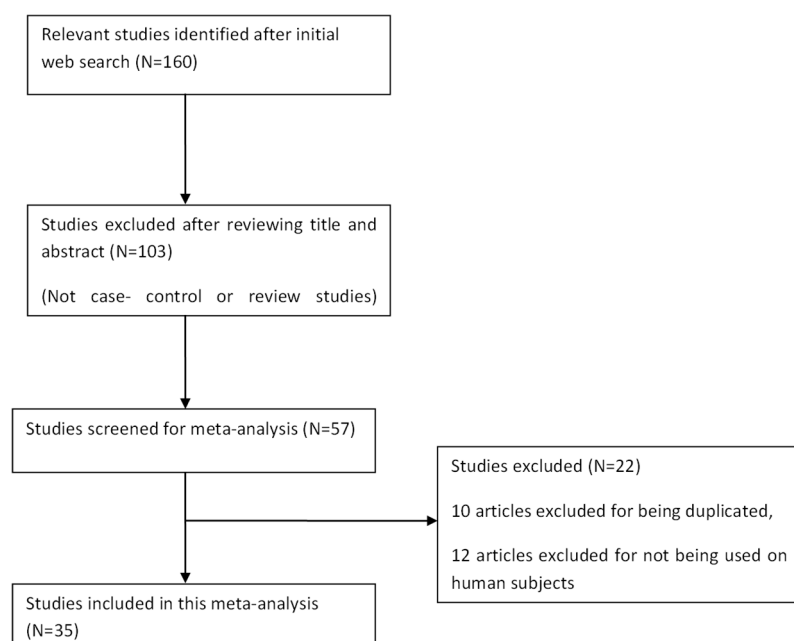


Fig. 1. PRISMA flow diagram: Demonstrating identification and study selection process

Table 1. Distribution of p53 codon 72 Arg>Pro polymorphism included in the meta-analysis

Authors	Years	Cancer Type	Control			Case			HWE P-value
			Arg/Arg	Arg/Pro	Pro/Pro	Arg/Arg	Arg/Pro	Pro/Pro	
Zahra Eyedian	2016	Lung	88	88	24	20	83	97	0.781
Fatemeh Keshavarz	2016	Breast	20	38	25	10	45	35	0.46
FarinazBehfarjam	2015	Prostate	35	44	17	68	21	7	0.624
SahArgohari-	2015	Breast	22	54	28	51	31	22	0.668
Mehdi Nikbahk	2015	CML	16	22	7	9	21	15	0.901
Hosseini-Asl	2015	Gastric	18	21	2	13	19	9	0.182
MinooYaghmae	2015	UterineLeiomyoma	53	72	24	36	65	38	0.956
Mehdi Nikbakht	2015	AML	7	48	4	20	36	3	0.000
Robab Sheikh	2014	Breast	51	88	41	72	76	32	0.7968
Mohammad Taheri	2014	Gastric	30	50	18	56	44	26	0.722
RoghayehDehghan	2014	Thyroid	8	24	8	4	22	14	0.205
Rahim Golmohammadi	2013	Breast	75	90	40	83	109	29	0.146
Boyajian	2013	Esophageal	38	37	17	36	36	15	0.171
MasomehFaghani	2012	Colorectal	162	217	86	34	47	10	0.376
Mohammad Ali	2012	Breast	5	13	2	12	7	1	0.140
Mohammad Ali	2012	Thyroid	19	40	41	16	42	41	0.111
Abbas Doosti	2011	Breast	41	29	19	55	64	10	0.003
Abbas Doosti	2011	Prostate	44	63	16	49	63	20	0.372
Mehdi Nikbahk	2011	Skin	58	77	28	46	63	23	0.777
Mehdi Nikbahk	2011	Skin	36	82	22	52	70	13	0.0301
Abbas Doosti	2011	Colorectal	6	11	3	8	10	2	0.575
Mohammad Mazani	2011	Gastric	27	58	15	6	88	10	0.07
Barzegar	2011	Gastric	31	57	12	31	48	21	0.067

Cntd. Table 2

Zahra Mojtahedi	2010	Head and Neck	28	85	27	49	78	18	0.011
Zahra Mojtaha	2010	Gastric	16	35	36	14	37	36	0.160
Zahra Mojtaha	2010	Colorectal	42	56	14	40	57	15	0.480
NasrinGhasem	2009	Endometrial	9	10	1	9	9	2	0.394
Mehdi Nikbahk	2009	Colorectal	58	77	28	28	54	10	0.777
Masoud Kazemi	2009	Breast	12	48	0	6	30	6	0.001
Mehdi Nikbahk	2008	Colorectal	4	21	7	2	15	13	0.066
MasomehFaghanin	2008	Breast	50	111	24	74	98	15	0.002
ParvizDeihim	2008	Oral squamous cell	52	66	32	35	38	11	0.202
BaharakKhadang	2007	Breast	30	50	19	19	31	10	0.821
Abdulmohammad	2006	Skin	76	113	61	97	101	52	0.142
SeyedAlireza	2006	Lung	15	51	14	29	49	2	0.013

Table 2. Result of heterogeneity and publication bias in the meta-analysis

Comparison	Heterogeneity analysis			Egger's linear regression test			Models
	Q	P	I <sup>2</sup> (%)	Intercept	95%CI	P	
Pro vs. Arg	58.38	0.005	41.8	-0.76	(-2.34,0.81)	0.33	Random
Pro/Pro vs. Arg/Arg	153.6	0.000	77.9	-0.15	(-2.16,1.86)	0.88	Random
Arg/Pro vs. Arg/Arg	91.87	0.000	63	0.26	(-1.51,2.04)	0.76	Random
Pro/Pro + Arg/Pro vs. Arg/Arg	164.2	0.000	79.3	0.88	(-1.48,3.26)	0.45	Random
Pro/Pro vs. Arg/Arg+ Arg/Pro	126.6	0.000	73.2	-0.11	(-2,1.78)	0.9	Random

**The association between p53 codon 72 Arg>Pro polymorphism and cancer risk**

To measure the association between p53 Codon 72 Arg>Pro polymorphism and cancer odds, all the 35 studies were pooled together (2426 cancer cases and 2928 controls). Pooled OR and 95% CI indicated no association between p53 Codon 72 Arg>Pro polymorphism and cancer odds in variant allele (Pro vs. Arg: OR= 1.075, 95%CI= 0.91 to 1.25, chi<sup>2</sup> (test odds ratio differs from 1) = 0.83, p= 0.36) and homozygous (Pro/Pro vs. Arg/Arg: OR= 0.911, 95%CI= 0.66 to 1.25, chi<sup>2</sup>= 0.32, p= 0.57). Similarly, recessive genetic model and dominant model were not associated with an increased odds of developing cancer (Pro/Pro vs. Arg/Arg+ Arg/Pro: OR= 0.91, 95%CI= 0.72 to 1.16, chi<sup>2</sup>= 0.49, p= 0.48), (Pro/Pro+Arg/

Pro vs. Arg/Arg: OR = 0.96, 95%CI= 0.74 to 1.24, chi<sup>2</sup>= 0.06, p= 0.8) (Figs. 2-6).

**Publication bias**

Begg's funnel plot and Egger's linear regression test were used to evaluate publication bias the included studies. The appearance of the shape of funnel plot and Egger's linear regression test did not show any evidence of publication bias among all comparison models (Table 2 and Figs. 7-11).

**Sensitivity analysis**

We performed sensitivity analysis to evaluate the effect

Odds ratio meta-analysis plot [random effects]

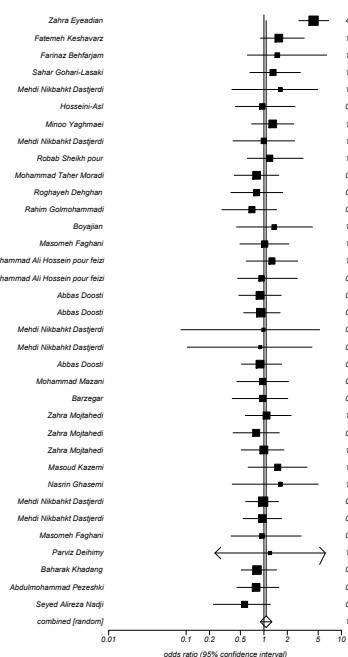


Fig. 2. Forest plot of odds ratio with 95% CI of overall cancer risk associated with p53 codon 72 Arg>Pro polymorphism for allele model

Odds ratio meta-analysis plot [random effects]

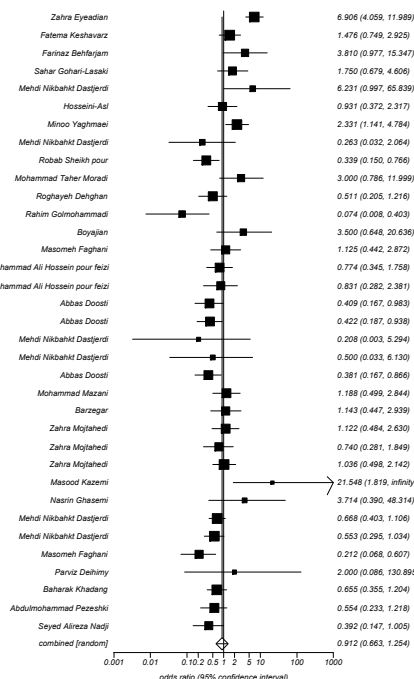


Fig. 3. Forest plot of odds ratio with 95% CI of overall cancer risk associated with p53 codon 72 Arg>Pro polymorphism for homozygous model

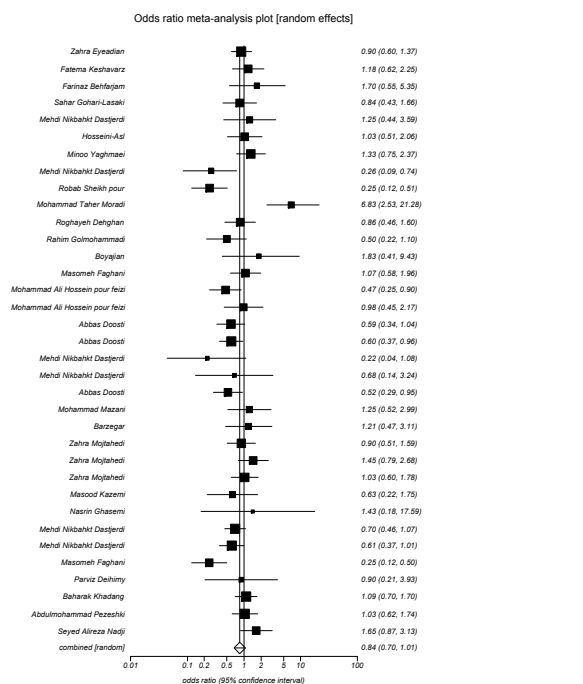


Fig. 4. Forest plot of odds ratio with 95% CI of overall cancer risk associated with p53 codon 72 Arg>Pro polymorphism for heterozygous model

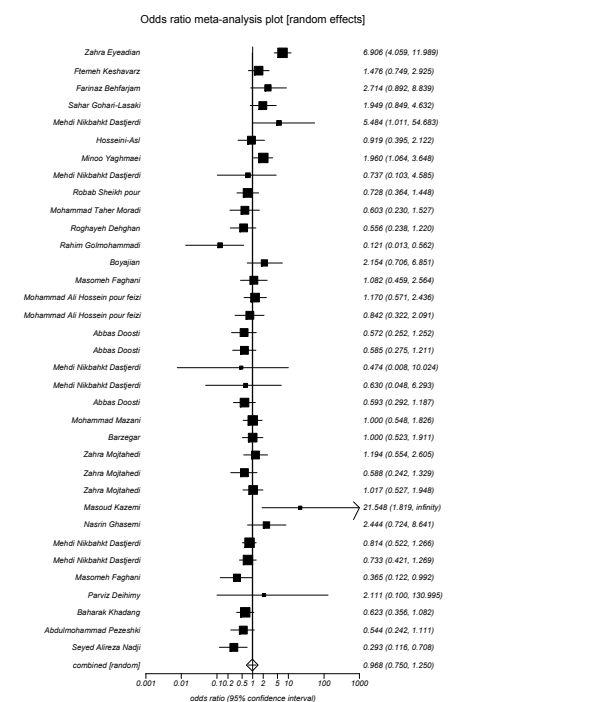


Fig. 6. Forest plot of odds ratio with 95% CI of overall cancer risk associated with p53 codon 72 Arg>Pro polymorphism for dominant model

### Discussion

Several epidemiological studies have indicated that cancer is a multi-factorial disease and that nutrition, use of

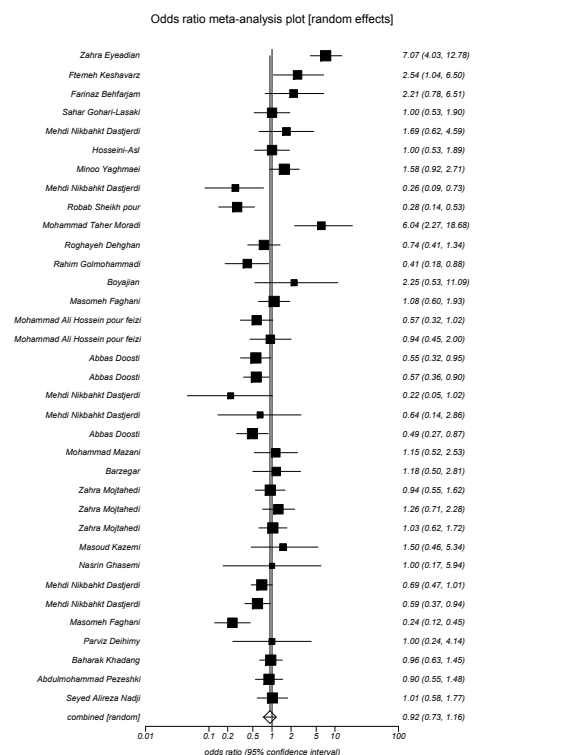


Fig. 5. Forest plot of odds ratio with 95% CI of overall cancer risk associated with p53 codon 72 Arg>Pro polymorphism for recessive model

of each study included in the present meta- analysis. The results of meta- analysis revealed that pooled ORs were generally similar in all the 5 models.

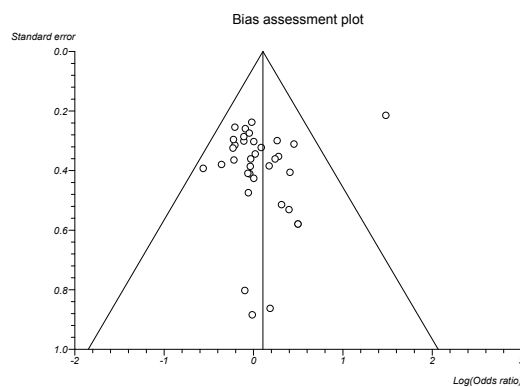


Fig. 7. Funnel plot detecting biases in the identification and selection of studies for allele dominant model

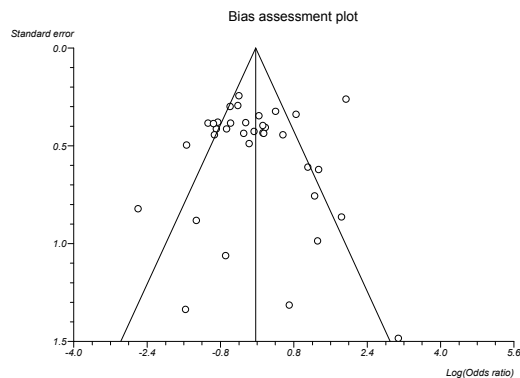


Fig. 8. Funnel plot detecting biases in the identification and selection of studies for homozygous dominant model

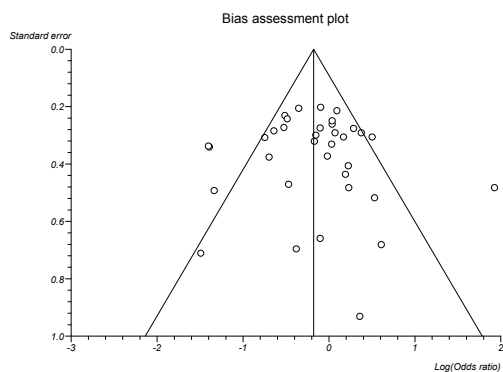


Fig. 9. Funnel plot detecting biases in the identification and selection of studies for heterozygous dominant model

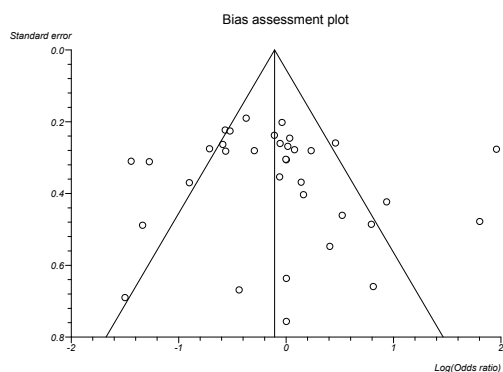


Fig.10. Funnel plot detecting biases in the identification and selection of studies for recessive dominant model

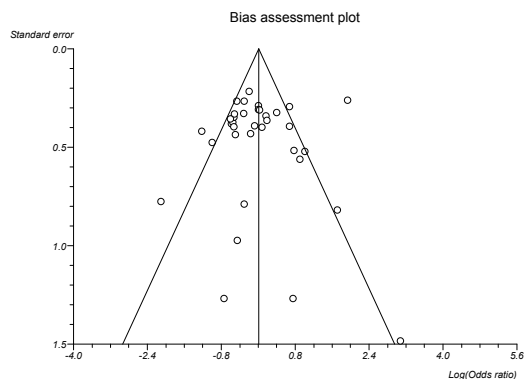


Fig. 11. Funnel plot detecting biases in the identification and selection of studies for dominant model

tobacco and/or alcohol, viral infections, genetic factors, and UV exposure are cancer risk factors. Furthermore, some genetic predisposing factors are involved in carcinogenesis. Genetic alteration could occur in oncogenes, tumor suppressors, and growth of regulator genes (25). TP53 is the most important tumor suppressor gene that plays an important role in response to DNA damage, so this is considered as "guardian of the genome". P53 is one of the most frequently mutated genes in human malignancies and more than 50% of human cancers (26). In addition to mutations, genetic polymorphisms could also have an effect on the P53 function. In particular, P53 Codon 72 (P53c72) single nucleotide polymorphism (SNP), which could result in either arginine (25) or proline (Pro) alleles,

creates 3 different genotypes: Arg/Arg, Arg/Pro, and Pro/Pro (27). The proteins p53Arg72 and p53Pro72 have dissimilar biochemical and biological possessions, for example, dissimilarity in the binding to parts of the transcriptional apparatus and dissimilarity in the initiation of transcription (10). The p53Arg72 protein persuades apoptosis faster and represses alteration more competently than the p53Pro72 protein (27). There have been reports showing possible involvement of P53c72 polymorphism in individuals' susceptibility to cancers including mouth cancer, breast cancer, thyroid cancer, colorectal, and prostate cancer, which seem to have a mutation in this gene (9, 11, 13, 14, 24). The mentioned case-control studies showed the contribution of P53c72 polymorphism to the carcinogenesis although these studies were done with a small sample size and the results from these individual studies lacked consensus. Thus, we performed the current meta-analysis with more number of cases and controls. Furthermore, to our knowledge, this was the first meta-analysis to assess the association of the P53c72 polymorphism with cancer susceptibility among Iranian population.

The overall pooled results of this meta-analysis revealed no association between variant allele of p53 c 72 G>C polymorphism with an increased or decreased cancer odds. Our results demonstrated that the p53 Codon 72 G>C polymorphism is not a significant cause of cancer odds among the Iranian population. Also, in the dominant model (Pro/Pro +Arg/Pro vs. Arg/Arg) codon 72 Arg>Pro polymorphism was not associated with a diminished odds of cancer among this population. A number of studies indicated that TP53 Arg72Pro have no influence on breast cancer odds (9, 28), colorectal cancer odds(29), and skin cancer odds (30), whereas some other studies revealed an association between this polymorphism with cancer odds; for instance, Doosti et al. reported that homozygous individuals with the Arg allele have a higher odds of developing breast cancer than heterozygote ones (31). Babaei et al. found that cases with Pro/Pro had an increased odds of developing prostate cancer compared to those with Arg/Arg (32). Similar to our result, no association was found in meta-analysis of p53 Codon 72 Arg>Pro polymorphism with cancer odds in Saudi and Indian population in all genetic models (33-35). This meta-analysis had some limitations. First, in the present study the p53 Codon 72 Arg/Pro polymorphism, which might have influenced the odds of cancer in combination with other genetic polymorphisms (gene-gene and gene-environment interaction), was not considered. Second, we found heterogeneity in the overall analysis. Third, our meta-analysis was based on unadjusted estimates, while a more precise analysis could be performed if individual data were available that would allow for an adjustment estimate (by age and sex). Despite these limitations, our meta-analysis had several strengths. First, the number of studies included in the analysis was relatively large. Second, we included studies published in English and Persian languages that covered all Iranian based publications.

**Conclusion**

A meta-analysis is an approach of statistical analysis,

which combines both statistically notable and none- statistically notable results from individual studies to improve statistical efficiency by enlarging the sample size. Our results revealed that p53 Codon 72 Arg>Pro polymorphism may considerably modulate the overall cancer odds among Iranian population.

### Acknowledgement

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### Conflict of Interests

The authors declare that they have no competing interests.

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