

## RESEARCH ARTICLE

# No Evidence of Association of the Arg72Pro p53 Gene Polymorphism with Cancer Risk in the Saudi Population: a Meta-Analysis

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## Abstract

**Background:** Earlier studies on the association between p53 codon 72 Arg>Pro polymorphism and cancer risk were inconclusive and conflicting for the Saudi population. Therefore, we performed a meta-analysis to investigate the relationship between the codon 72 Arg>Pro polymorphism and overall cancer risk in Saudi Arabia. **Materials and Methods:** We searched all eligible published studies and data were pooled together to perform the meta-analysis. Pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for homozygous, heterozygous, dominant and recessive genetic models. **Results:** A total of five eligible published studies covering 502 cancer cases and 784 healthy controls were included in the meta-analysis. No publication bias was detected in this study. The results suggested that the variant (Pro vs Arg: p=0.960; OR=1.004, 95% CI=0.852-1.183), homozygous (Pro.Pro vs Arg.Arg: p=0.970; OR=1.006, 95% CI=0.729-1.390), heterozygous (Arg.Pro vs Arg.Arg: p=0.473; OR=0.783, 95% CI=0.402-1.527) carriers were not associated with overall cancer risk. Similarly, dominant (Pro.Pro+Pro.Arg vs Arg.Arg: p=0.632; OR=0.886, 95% CI=0.540-1.454) and recessive (Pro.Pro vs Pro.Arg+Arg.Arg: p=0.269; OR=1.163, 95% CI=0.890-1.521) models also did not indicate increased risk of cancer. **Conclusions:** The current meta-analysis suggests that the codon 72 Arg>Pro polymorphism of the p53 gene might not contribute to cancer susceptibility in Saudi population. Future well designed large case control studies are needed to validate our findings.

**Keywords:** Meta-analysis - p53 polymorphism - cancer - Saudi Arabia

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## Introduction

Cancer is a most dreadful disease for humankind and leading cause of death worldwide (Jemal et al., 2011). Despite its low incidence rate as compared to western countries, it still continues to be a major problem in Saudi Arabia (Saudi Cancer Registry, 2014). Cancer is a multifactorial disease and its incidence rate varies among worldwide due to variation of geographical region, habitats and genomic frequency (Pharoah et al., 2004). Epidemiological studies suggest that the majority of cancers is polygenic and several genes with modest effect are involved in development of carcinogenesis (Vineis, 2004; Verit and Yucel, 2013). Thus, identification of genetic risk markers related to cancer risk is important, as it may allow for the creation of early diagnostic factors for individual and population risks, and helps in the understanding of pathophysiological mechanisms of carcinogenesis.

TP53 protein, encoded by p53 gene (TP53 at 17p13) is a tumor suppressor gene which is involved in various cellular processes, such as cell cycle arrest, senescence, apoptosis, inhibition of tumorigenesis and protects the genomic integrity (Suzuki and Matsubara, 2011; Al-Fatlawi et al., 2014). p53 gene is mutated in 50-70% in human cancers (Suzuki and Matsubara, 2011; Shin and Kim, 2014), and alter expression of p53 in serum is associated with various malignant tumors (Rivlin et al., 2011; Dunna et al., 2012), which highlights the significance role of p53 in malignancy.

During past decades, numbers of genetic polymorphism in p53 locus have been widely investigated for their effect in different cancer risks (Liu et al., 2014; Rao et al., 2014; Pouladi et al., 2014), among them the most common polymorphism is at codon 72 (Arg72Pro) (G>C) (rs1042522) This codon which is found at exon 4 of the p53 gene and is frequently studied worldwide (Vijayaraman et al., 2012; Xiang et al., 2012; Kafshdooz

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et al., 2014). At codon 72, arginine to proline substitution altered the p53 gene translation product, resulted in a reduced capacity of DNA repair, cell cycle regulation, apoptosis and thereby increased the susceptibility of cancer risk (Grochola et al., 2010).

The significance of p53 gene in carcinogenesis, has considered codon 72 Arg>Pro polymorphism, could be a potential predictive marker for prevention and early intervention of cancers (Hrstka et al., 2009). Also, genetic variant of p53 gene appears as good resources to study inter individual differences in cancer risk and therapeutic response (Lin et al., 2008).

Many studies have investigated the role of p53 codon 72 Arg>Pro polymorphism in many types of cancers in Saudi population, but the results is remaining inconclusive or inconsistent (Siraj et al., 2008; Alshatwi et al., 2012; Al-Hadyan et al., 2012; Al-Qasem et al., 2012; Alsbeih et al., 2013). An individual study might have small sample size and not be powered sufficiently to detect a small effect of this polymorphism on cancer susceptibility. Meta-analysis is a powerful tool to combine the data from individual studies and provide robust conclusion (Mandal et al., 2013). Therefore, we performed a meta-analysis from all eligible case-control studies to clarify the relationship between p53 codon 72 Arg>Pro polymorphism and cancer risk in Saudi population.

## Materials and Methods

### Identification and eligibility of relevant studies

We have followed “PRISMA” 2009 checklist criteria for meta-analysis. We carried out a PubMed (Medline), EMBase, Cochrane, Google (scholar) web database search covering all research articles published (including personal communication) using following key words, “p53 gene polymorphism”, “p53 gene mutation”, “p53 gene variant” and “cancer”, “carcinoma”, “risk”, “tumor susceptibility” in Saudi population (last updated on December 2014). All the searched studies were retrieved and the reference lists were checked for any other relevant studies.

### Inclusion and exclusion criteria

To minimize the bias and heterogeneity to interpretation of our results, studies included in the current meta-analysis had to meet all the following criteria: (i) evaluation of the p53 codon 72 Arg>Pro, and cancer risk, (ii) use of a case-control design, (iii) recruitment of pathological confirmed cancer patients and cancer-free controls, (iv) and the available genotype frequency. Additionally, when the case-control study was included by more than one article using the same case series, we selected the study that included the largest number of individuals. The major criteria for exclusion of studies were (i) overlapping data and (ii) only case reported studies, (iii) genotype frequency missing, (iv) family based studies, and (v) review articles.

### Data extraction and quality assessment

For each publication, the methodological quality assessment and data extraction were independently abstracted in duplicate using a standard protocol and according to the inclusion criteria by two independent

authors (MI and RKM). Disagreement between the authors was resolved after discussion among the authors. The following information was sought from each article: the year of publication, the number of cases and controls, type of study, genotype frequencies, and the Hardy-Weinberg (HWE).

### Statistical analysis

We calculated the odds ratio (OR) and corresponding 95% confidence interval (CI), to evaluate the association between the p53 codon 72 Arg>Pro polymorphism and cancer risk. Heterogeneity assumption was checked by the chi-square-based Q-test (Wu and Li, 1999). A p-value (<0.05) for the Q-test indicates a lack of heterogeneity among the studies, and then the pooled OR was calculated by the fixed effects model (Mantel and Haenszel, 1959); otherwise, the random-effects model was used (DerSimonian and Laird, 1986). In addition, I<sup>2</sup> statistics was used to quantify inter study variability. It ranges between 0% and 100%, where a value of 0% indicates no observed heterogeneity, and larger values indicate an increasing degree of heterogeneity (Higgins et al., 2003). The HWE was examined in the control subjects using a goodness-of-fit chi-square test for each study. Publication bias was assessed by visual inspection of funnel plots in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot suggests a possible publication bias. Funnel plot asymmetry was also assessed by the Egger’s linear regression test. The significance of the intercept was determined by the t-test (p<0.05) which was considered representative of statistically significant publication bias (Egger et al., 1997). All statistical analysis for meta-analysis was performed by comprehensive meta-analysis (CMA) V2 software (Biostat). CMA V2 has several advantages over other software available for computing meta-analyses (<http://metaanalysis.com/pages/comparisons.html>).

## Results

### Characteristics of published studies

Nineteen articles were recovered by literature search. All retrieved articles were reviewed by reading the title, abstract and the full texts for the potentially relevant publications and further checked for their suitability for this meta-analysis. We excluded 14 articles because their study designs were not matched with our inclusion criteria (Figure 1). Studies using the p53 codon 72 Arg>Pro polymorphism to predict survival risk in cancer or considering indicators for response to therapy were excluded. Studies to investigate the levels of p53 mRNA or p53 codon 72 Arg>Pro protein expression were also excluded. We included only case-control studies. After careful screening, finally five eligible published studies were included in this study (Table 1). The distribution of genotypes, MAF and HWE is tabulated in Table 2.

### Evaluation of potential publication bias

The Begg’s funnel plot and Egger’s test were performed to access the publication bias of literatures included for meta-analysis. The shape of funnel plots and

**Table 1. Main Characteristics of All Five Studies Included In The Meta-analysis**

| Authors and year       | Types of cancer   | Study design | Genotyping method | Control | Cases |
|------------------------|-------------------|--------------|-------------------|---------|-------|
| Alsbeih et al., 2013   | Cervical          | HB           | Sequencing        | 100     | 100   |
| Alshatwi et al., 2012  | Breast            | HB           | Taq Man           | 100     | 100   |
| Al-Hadyan et al., 2012 | Head and Neck     | HB           | Sequencing        | 251     | 156   |
| Al-Qasem et al., 2012  | Breast            | HB           | Sequencing        | 108     | 100   |
| Siraj et al., 2008     | Papillary thyroid | HB           | PCR-RFLP          | 225     | 46    |

\*SCCHN, Squamous cell carcinomas of the head and neck, HB, Hospital based

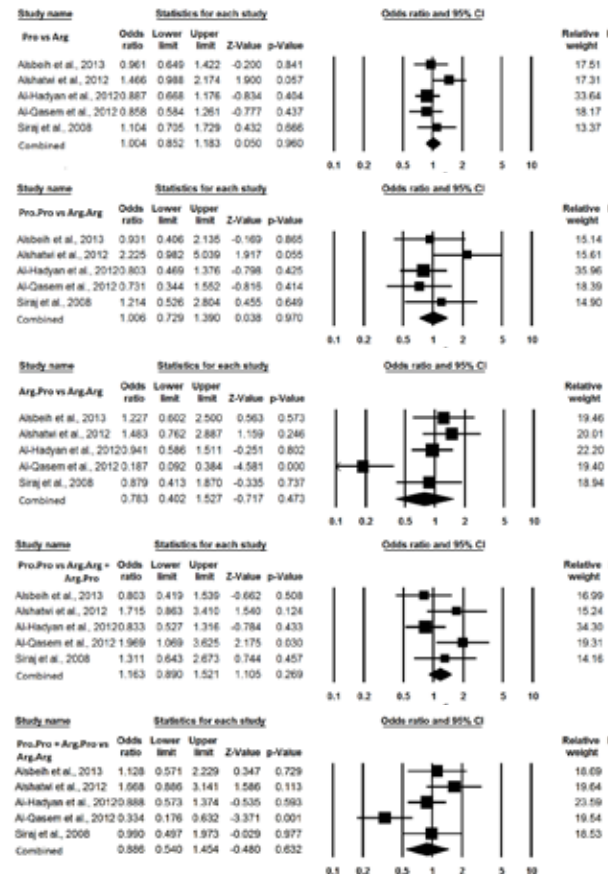
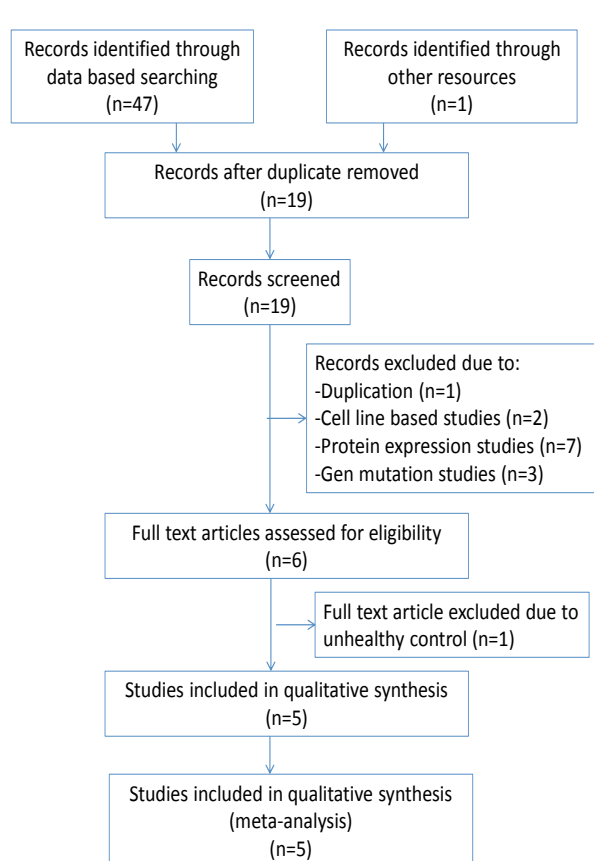
**Table 2. Genotypic Distribution of p53 (72) Gene Polymorphism Included in Meta-analysis**

| Authors and year       | Controls      |               |               |                     | Cancer cases  |               |               |                     | HWE<br>p value |
|------------------------|---------------|---------------|---------------|---------------------|---------------|---------------|---------------|---------------------|----------------|
|                        | Genotype      |               |               | Minor allele<br>MAF | Genotype      |               |               | Minor allele<br>MAF |                |
|                        | GG<br>Arg.Arg | GC<br>Arg.Pro | CC<br>Pro.Pro |                     | GG<br>Arg.Arg | GC<br>Arg.Pro | CC<br>Pro.Pro |                     |                |
| Alsbeih et al., 2013   | 22            | 52            | 26            | 0.52                | 20            | 58            | 22            | 0.51                | 0.67           |
| Alshatwi et al., 2012  | 32            | 51            | 17            | 0.42                | 22            | 52            | 26            | 0.52                | 0.66           |
| Al-Hadyan et al., 2012 | 71            | 110           | 70            | 0.49                | 48            | 70            | 38            | 0.46                | 0.05           |
| Al-Qasem et al., 2012  | 19            | 65            | 24            | 0.52                | 39            | 25            | 36            | 0.48                | 0.03           |
| Siraj et al., 2008     | 68            | 105           | 52            | 0.46                | 14            | 19            | 13            | 0.48                | 0.35           |

\*MAF, Minor allele frequency, HWE, Hardy Weinberg equilibrium

**Table 3. Statistics to Test Publication Bias and Heterogeneity in Meta-analysis**

| Comparisons                | Egger's regression analysis |        |      | Heterogeneity analysis |                |                    | Models for meta-analysis |
|----------------------------|-----------------------------|--------|------|------------------------|----------------|--------------------|--------------------------|
|                            | Intercept                   | 95% CI | p    | Q value                | Pheterogeneity | I <sup>2</sup> (%) |                          |
| Pro vs Arg                 | 3.12                        | -19.86 | 0.39 | 5.13                   | 0.27           | 22.09              | Fixed                    |
| Pro/Pro vs Arg/Arg         | 3.03                        | -17.31 | 0.34 | 5.21                   | 0.26           | 23.25              | Fixed                    |
| Arg/Pro vs Arg/Arg         | -2.53                       | -40    | 0.71 | 20.93                  | <0.0001        | 80.89              | Random                   |
| Pro/Pro+Arg/Pro vs Arg/Arg | 0.25                        | -32.7  | 0.96 | 13.41                  | 0.009          | 70.18              | Random                   |
| Pro/Pro vs Arg/Arg+Arg/Pro | 4.05                        | -22.08 | 0.32 | 7.48                   | 0.11           | 46.56              | Fixed                    |



**Figure 1. Flow Diagram of the Study Selection Process**

**Figure 2. Genetic Modeling and Risk for Cancer**

Egger's test did not show any evidence of publication bias in our meta-analysis (Table 3).

#### Test of heterogeneity

Heterogeneity was observed in two genetic models, heterozygous (GC vs GG) and dominant (CC+GC vs GG) which were included for the analysis. Hence, the random effects model was used for calculation of OR and 95%CI.

#### Association of p53 codon 72 Arg>Pro gene polymorphism and overall cancer susceptibility

We pooled all the five studies together, which comprise of 784 controls and 502 cancer cases to assess the overall association between the p53 codon 72 Arg>Pro polymorphism and cancer risk. The results indicated that codon 72 Arg>Pro polymorphism might not be associated with an increased or decreased risk of developing cancer among Saudi population in all analyzed genetic models, such as allelic (Pro vs Arg:  $p=0.960$ ; OR=1.004, 95% CI=0.852-1.183), heterozygous (Arg.Pro vs Arg.Arg:  $p=0.473$ ; OR=0.783, 95% CI=0.402-1.527) and homozygous (Pro.Pro vs Arg.Arg:  $p=0.970$ ; OR=1.006, 95% CI=0.729-1.390) comparisons. Similarly, dominant (Pro.Pro+Arg.Pro vs Arg.Arg:  $p=0.632$ ; OR=0.886, 95% CI=0.540-1.454) and recessive (Pro.Pro vs Arg.Pro+Arg.Arg:  $p=0.269$ ; OR=1.163, 95% CI=0.890-1.521) genetic models also were not associated with an increased risk of developing cancer (Figure 2).

## Discussion

During last decades, cancers researcher has led interest to the association between single nucleotide polymorphism (SNPs) and cancer susceptibility (Alsbeih et al., 2010; Nassiri et al., 2013). P53 gene is a multifunctional tetrameric transcription factor involved in many important biological processes (Levine and Oren, 2009). The codon 72 polymorphism, the most common SNP in the TP53 gene, located in the non-conserved proline-rich region of exon 4 (Aizat et al., 2011). This polymorphism encodes either arginine (CGC) or proline (CCC) and is functionally important in growth suppression and apoptosis (Katkoori et al., 2009). The frequency of this polymorphism also varies among different races and ethnic groups (Murphy, 2006). Inter-individual variation in apoptotic capacity is largely attributed to an individual's genetic constitution, and genetic variation of apoptosis related genes may affect the expression of proteins and associated with the risk and prognosis of many cancers (Pathak et al., 2014).

Given the important roles of p53 in carcinogenesis, it is reasonable to speculate that host genomic polymorphism of p53 gene may affect the tumor occurrence. Recently, Genetic variants of the p53 codon 72 Arg>Pro polymorphism and its role in the etiology of several cancers have been studied extensively in Saudi population, but the results are inconclusive.

Among the five eligible studies, two studies reported statistical significance risk association of Pro allele of p53 codon 72 in breast and head and neck cancer respectively (Alshatwi et al., 2012; Al-Hadyan et al., 2012). The present meta-analysis results indicated that p53 codon 72 Arg>Pro polymorphism did not have statistically significant

relationship between overall cancer susceptibility in Saudi population. Individual carrying the Pro allele did not exhibit any risk of cancer in all the eligible genetic models, when compared with individual carrying the Arg allele. Thus, it is possible that codon 72 Arg>Pro analyzed variant do not influence individual cancer risk. Similar to our result, no association was reported in meta-analysis of p53 codon 72 Arg>Pro polymorphism and risk of cervical cancer (Zhou et al., 2012), breast cancer (Hou et al., 2013), head and neck squamous cell carcinoma (Xia et al., 2012; Ren et al., 2014). Although, recently significant association was reported Arg>Pro polymorphism in thyroid carcinoma under the recessive model in Asian population (Wang et al., 2014). Cancer is a multistep process and a single genetic variant is usually insufficient to predict risk of this deadly disease that has a complex disease phenotype. Gene polymorphisms are complicated and fluctuating, which mainly attributed to different ethnicities.

There are some limitations to our meta-analysis that should be considered when interpreting the results. First, present assessment was based on unadjusted estimates because of data limitations. Second, the number of studies included in the analysis was relatively small. Third, gene-gene and gene-environment interaction was not performed.

Despite these limitations, however, our meta-analysis has important advantages. First, the substantial number of cases and controls are included in this meta-analysis significantly increased the statistical power of this analysis as compare to individual study. Second, we did not have publication bias in the included studies, which possibly, suggest the reliability of our results.

In conclusion, our meta-analysis evaluated the relationship between the p53 codon 72 Arg>Pro polymorphism and cancer risk and revealed that the p53 codon 72 Arg>Pro polymorphism might not statistically modulate the overall cancer risk in Saudi population. Further larger studies are warranted to clarify the role of this polymorphism in the pathophysiology of cancer.

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