Arg72Pro polymorphism in P53 gene and Breast Cancer Risk Population: a meta-analysis of case-control studies matched

Brehima Diakite (✉ br.diakite@yahoo.fr)

Universite des Sciences des Techniques et des Technologies de Bamako <https://orcid.org/0000-0001-8296-5292>

Yaya Kassogue

University des Sciences, techniques et Technologies de Bamako

Guimogo Dolo

Faculty of Medicine and Odontostomatology/ Universite des Sciences, Techniques et Technologies de Bamako

Jun Wang

Northwestern University

Erin Neuschler

University of Illinois Chicago

Oumar Kassogue

Universite des Sciences, Techniques et Technologies de Bamako

Mamadou Keita

CHU du Point G

Cheick Bougari Traore

Faculty of Medicine and Odontostomatology/Universite des Sciences, Techniques et Technologies de Bamako

Bakarou Kamate

Universite des Sciences, Techniques et Technologies de Bamako

Etienne Coulibaly

Northwestern University Department of Biomedical Engineering

Nadifi Sellama

Universite Hassan II Casablanca

Robert Murphy

Northwestern University Department of Biomedical Engineering

Seydou Doumbia

Universite des Sciences, techniques et Technologies de Bamako

Lifang Hou

Northwestern University Department of Biomedical Engineering

Mamoudou Maiga

Northwestern University Department of Biomedical Engineering

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Abstract

Background The effect of the Arg72Pro variant of the P53 gene on the risk of developing breast cancer remains variable in populations. However, using strategies like grouping age-matched controls with disease cases may provide a strong meta-analysis. Our goal was to perform a meta-analysis in order to study the association of Arg72Pro variant of P53 gene and breast cancer.

Methods Databases such as PubMed, Genetics Medical Literature, Harvard University Library, Web of Science and Genesis Library were used to search articles. Age-matched control studies on breast cancer that evaluated the genotype frequencies of the Arg72Pro P53 gene were selected. Fixed and random effects (Mantel-Haenszel) were calculated using pooled odds ratio of 95% CI to determine the disease risk. Hardy-Weinberg equilibrium test was used to measure deviation in the distribution of genotypes in controls. Inconsistency was calculated to determine heterogeneity among the studies. Estimated publication bias was performed through the funnel plot and Egger's test.

Results Nine publications with controls age-matched cases including 4684 disease cases and 4636 controls were evaluated in this meta-analysis, all were in the Caucasian population. Our results suggested that Arg72Pro P53 was associated with a risk for breast cancer in the dominant model (Pro/Pro+Arg/Pro vs. Arg/Arg: OR= 1.16, 95% CI = 1.04-1.31) and the additive model (Pro vs. Arg: OR= 1.13, 95% CI = 1.03-1.24, P= 0.007), but not in the recessive model (Pro/Pro vs. Arg/Arg + Arg/Pro, OR = 1.18, 95% CI = 0.96-1.44; P= 0.12).

Conclusions This meta-analysis found significant association between the Arg72Pro polymorphism in the P53 gene and the breast cancer risk. Individuals carrying at least one Pro allele of the P53 gene are more likely to have breast cancer with dominant and additive models than individuals carrying the Arg allele.

Background

Breast cancer, a genetic disease, is the leading cause of death among women around the world, and thus represents a major public health challenge [1]. According to the International Center for Research on Cancer (CIRC), 1.38 million new cases of breast cancer were detected worldwide in 2008 [2] against 1.15 million cases in 2002 [1]. The incidence of breast cancer differs among different populations in the world [3]. In recent decades, spectacular progress has been made in understanding the molecular genetics of breast cancer pathology. In addition to the direct involvement of genetic predisposition genes, other genes participating in cell division regulation are also implicated in the occurrence of breast cancer [4-5], such as P53 gene, a tumor suppressor gene. While the role of P53 gene is not fully elucidated yet, it is recognized that P53 plays a key role in the regulation of cell proliferation and apoptosis. The P53 protein is essential to maintain the integrity of the cell and its components. In human cancers, mutated P53 produces abnormal proteins that alter or inhibit transcriptional regulation [6]. Consequently, a cell cannot respond to stress, and the cell cycle as well as apoptosis are inhibited. Genomically, inactivation or

mutation of P53 gene would be responsible for a linkage disequilibrium in the DNA sequence leading to genomic instability [7]. These abnormalities of P53 gene protein associated with chromosomal aberrations could induce the development of breast and ovarian cancer [8]. This gene is known to be the most frequently mutated in human cancers [9]. The gene is located on chromosome 17p13 and contains 11 exons. Several polymorphisms have been identified, but the most widely studied variant is the substitution of Arginine by Proline at position 72. Arg72Pro variant is located in exon 4, and has been shown to be associated with many pathologies including cancer [10-11]. Although many association studies on candidate genes have investigated the relationship between the Arg72Pro variant of the P53 gene and the risk of breast cancer, the reports from these studies remain contradictory. Some studies have shown that Arg72Pro gene is associated with the risk of breast cancer, while others found no associations. The studies carried out by Menzel *et al.* 2004 [12] and Akkiprik *et al.* 2009 [13] have shown a link between Arg72Pro and breast cancer risk in the Caucasian populations. However, another age-unmatched case-control study in the similar population concluded that Arg72Pro P53 was not associated with the risk of breast cancer [14]. This inconsistency in the relationship between Arg72Pro P53 gene and breast cancer risk may be explained by a very high heterogeneity in the frequency of mutations. This heterogeneity is likely related to the geographical origin of patients, the ethnicity [15-17] and the age-unmatched controls with patients' group of the same population. In view of all these observations, the present meta-analysis will include only studies with age-matched controls with patients, to qualitatively assess the effect of Arg72Pro on the risk of breast cancer in the Caucasian population.

Methods

Literature search

The Pubmed Genetics Medical Literature Database, the Harvard University Library, and the Web of Science and Genesis Library were used to identify available articles published in English. The keywords "P53", "Arg72Pro" and "polymorphism" or "mutation" or "gene" and "breast cancer" cited in the genetic association studies were used to detect and select scientific manuscripts in these databases. We also reviewed references cited in these studies to identify additional articles that were not identified by our research in the databases.

Inclusion criteria

The inclusion criteria were: (1) published case-control studies as an original article to evaluate the association between Arg72Pro polymorphism of the P53 gene and risk of breast cancer, (2) full manuscript available, (3) case-control study with age-matched, (4) distribution of genotype respecting Hardy-Weinberg equilibrium (HWE) in controls, (5) availability of the three genotypic frequencies (Arg/Arg, Arg/Pro and Pro/Pro) in the case and control groups. (6) Three investigators independently evaluated each study to determine eligibility.

Data extraction

The data was collected by an investigator and verified by a second investigator to reach consensus on all points. First author, year of publication, country, ethnicity of study population, sample size, age-matched, distribution of genotype and alleles, as well as the recalculation of HWE in controls were extracted from the eligible studies. A third reviewer made a contradictory assessment to reconcile the assumptions. The data of controls evaluated with Arg72Pro variant were included in this meta-analysis.

Statistical analysis

Chi² analysis with P<0.05 significance level was used to evaluate whether Arg72Pro polymorphism distribution of the P53 gene in controls fits Hardy-Weinberg equilibrium (HWE). The association between the variant Arg72Pro and the risk of breast cancer was evaluated by the Odd ratio (OR) of 95% CI. Evaluation of the association strength of Arg72Pro polymorphism of P53 gene was made with the genetic models: dominant (Pro/Pro + Arg/Pro vs. Arg/Arg), recessive (Pro/Pro vs. Arg/Arg+Arg/Pro) and additive (Pro vs. Arg). The hypothesis of heterogeneity among the studies was assessed by I² statistical test [18-19]. If I²> 50% (presence of heterogeneity), the random effects model was used to calculate the overall OR, otherwise (lack of heterogeneity), the fixed effects method has been used. We also have examined the funnel plot to determine publication bias [20]. All statistical analyses were performed with Review Manager Software version 5.1.

Results

In the light of our results, 87 case-control studies from the literature search (Fig. 1) that investigated the association of Arg72Pro of P53 gene in the context of breast cancer were included, of which only 26 studies had a genotype distribution of control population that met Hardy-Weinberg equilibrium, and 9 out of the 26 studies have age-matched controls, all of which were from Caucasian populations (Table 1). This analysis was very selective with a total of seventy-eight studies that did not meet inclusion criteria of this meta-analysis. Genotype distribution of the control population that met Hardy-Weinberg equilibrium was a minimum requirement for studies to be included.

Figure 1. Flow diagram of the studies evaluated for meta-analysis

Table 1. Distribution of Arg72Pro P53 gene in breast cancer cases and age-matched controls in studies included in this meta-analysis

Quantitative Analysis

The grouped analysis according to the genetic models is summarized in Table 2. A significant association between Arg72Pro of P53 gene and the risk for breast cancer was observed in the dominant model (OR= 1.16, 95% CI = 1.04-1.31; P= 0.01) and the additive model (OR= 1.13, 95% CI = 1.03-1.24, P= 0.007), but not in the recessive model OR = 1.18, 95% CI = 0.96-1.44; P= 0.12).

Tableau 2 Distribution of Arg72Pro P53 gene according to the genetic models

Genetic	Fixed effect	Heterogeneity Test		
Models	Pooled OR (95% CI)	P	I ²	p'
Dominant	1.16 (1.04-1.31)	0.01*	27%	0.20
Recessive	1.18 (0.96-1.44)	0.12	0%	0.52
Additive	1.13 (1.03-1.24)	0.01*	34%	0.14

*: Significant, P: p value OR, p': p value heterogeneity; I²: Inconsistency; dominant: Pro/Pro + Arg/Pro vs. Arg/Arg; recessive: Pro/Pro vs. Arg/Arg+Arg/Pro; additive: Pro vs. Arg

Test for Heterogeneity

After elimination of studies deviating from Hardy-Weinberg equilibrium in controls, no evidence of heterogeneity (I²> 50%) was found with the dataset analyzed in the different genetic models. According to the genetic models, the fixed effects models (p <0.05 for Q test) were used for the interpretation of the pooled OR in this meta-analysis (Table 2) (Supplementary material). In addition, we compared the pooled OR of the fixed and random effects, and found no statistically significant difference between the two effects, which supports strongly the consistency of the present study's data.

Analysis's Influence

To maintain the stability of the meta-analysis after the non-inclusion of deviant studies of HWE and sensitivity analysis, we evaluated the influence of each study on pooled OR. No study has shown a significant influence of the pooled OR effect in each of the different genetic models (Table 2).

Publication Bias

The publication bias has been evaluated using the funnel plot. After excluding studies that disagree with the Hardy-Weinberg equilibrium in controls and the sensitivity analysis, no significant publication bias was found in dominant, recessive and additive models (Figure 2).

Figure 2. Funnel plots of dominant (a), recessive (b) and additive (c) models precision by OR

Discussion

Breast cancer is a multifactorial disease and its occurrence depends on the synergistic action of clinical, biological and environment factors and mechanisms [27-28]. In addition to these risk factors, the role of specific genes in the pathology of breast cancer is increasingly evident. The P53 gene encodes a transcription factor that binds to DNA and promotes the expression of genes that would repair cellular damage. Therefore, P53 is a tumor suppressor that sounds the alarm when DNA damage prevents the cell from turning into a cancer cell, or even inducing cell death. In the presence of a mutation, P53 gene can no longer repair the damaged DNA, which will lead to appearance of the malignant cells responsible for tumorigenesis [29-30]. In the recent decade, many studies have been conducted to assess the correlation between the polymorphism of the Arg72Pro P53 gene and the risk of breast cancer. However, these results remained very often contradictory. The meta-analysis can be an adequate tool to detect the effect of a gene in diseases with a great power of confidence. This meta-analysis evaluated the association between the variants Arg72Pro of the tumor suppressor P53 gene and breast cancer with eligibility criteria of case-control studies that had age-matched controls in HWE. All nine studies included were from the Caucasian population. Although, inclusion of other ethnic groups would be interesting, we believe that inclusion of ethnically non-biased studies improves the accuracy of our analysis.

Our results suggested a strong positive association between the Arg72Arg variant of the P53 gene and breast cancer risk. This risk was found to be 1.16 fold in the dominant genetic model and 1.13-fold in the individuals carrying the Pro allele. In addition, this work showed that, the recessive model had no protective effect against the development of breast cancer. These results were consistent in part with those of Hou *et al.* 2013 [31], who found in a similar study population that individuals carrying Pro allele in the dominant (OR=1.036, 95%: 0.927-1.159), recessive (OR = 1.019, 95% CI: 0.916- 1.134) and additive (OR = 1.002, 95%, 0.972-1.033) models were not protected from the disease. Goncalves *et al* 2013 [32] also found the same result as ours with the dominant model. However, this present meta-analysis was discordant with those of Zhuo *et al.*'s work that showed that the Pro allele of P53 gene was not associated with the occurrence of breast cancer [33]. The difference between our results can be explained by the presence of heterogeneity with the three genetic models, and the mixture studies with age-matched controls and unmatched controls in their analysis. Their studies also included studies whose controls were not in HWE [34-35]. The great and rigorous selection of these inclusion criteria is in fact the innovation in our present study. In addition, the meta-analyses of Goncalves *et al.* 2013 [32], He *et al.* 2011 [36] and Ma *et al.* 2011 [37] showed that the Arg allele of the P53 gene was not associated with the risk of breast cancer, which is consistent with our findings.

The literature is composed of contradictory conclusions regarding the association of Arg72Pro P53 gene with breast cancer risk, but most of the previous meta-analyses focused on the presence or absence of the wild-type (Arg) allele in these genetic models: dominant (Arg/Arg+Pro/Arg vs. Pro/Pro), recessive (Arg/Arg vs. Arg/Pro+Pro/Pro) and additive (Arg vs. Pro) [32, 36-37]. However, we have found some bias in certain studies with regard to the inclusion criteria of scientific articles, which may have influenced

those meta-analyses and interpretations. This bias existed in mostly studies whose distribution of Arg/Arg, Arg/Pro and Pro/Pro genotypes in controls was not in HWE [34, 35, 38-49].

Conclusions

In the light of this meta-analysis, individuals carrying at least one Pro allele of the P53 gene are more likely to have breast cancer with dominant and additive models than individuals carrying the Arg wild-type allele. Our study further reinforced and confirmed the hypothesis that the P53 gene is usually mutated in about half of breast cancer cases. For the stability and homogeneity of results from meta-analysis, future similar studies must consider criteria for selecting articles such as the HWE agreement and controls age-matched cases studies. Future studies should also consider comparing different ethnic groups.

Declarations

Abbreviations

Arg: Arginine; CI: Confidence interval, CIRC: International Center for Research on Cancer; Fig.: Figure; HWE: Hady-Weinberg Equilibrium; I^2 : Inconsistency; N: Number; OR: Odd ratio; P: P value Pro: Proline.

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Availability of data and materials

The dataset analyzed for this study is available from the table 1.

Authors' contributions

All authors read and approved the final manuscript. Study concept and design: BD, YK, MK, CBT, JW, EN, ED, CBT, BK, SN, GD, SD, LH, MM. Acquisition of data: BD, YK

. Analysis and interpretation of data: BD, YK, MM. Drafting of the manuscript: BD with assistance from by YK, MM. Critical revision of the manuscript for important intellectual content: JW, EN, SN, GD, SD, LH. Obtaining supervision: RM..

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Distribution of Arg72Pro P53 gene in breast cancer cases and age-matched controls in studies included in this meta-analysis

Authors	Cases				Controls				p
	N	Arg/Arg	Arg/Pro	Pro/Pro	N	Arg/Arg	Arg/Pro	Pro/Pro	
Akiprik <i>et al.</i> 2009 [13]	95	25	50	20	107	46	49	12	0.85
Buyru <i>et al.</i> 2003 [21]	115	64	39	12	63	26	28	9	0.74
Cherdyntseva <i>et al.</i> 2012 [22]	388	184	162	42	275	148	100	27	0.10
Costa <i>et al.</i> 2008 [23]	175	98	61	16	212	124	70	18	0.08
Denisov <i>et al.</i> 2009 [24]	297	148	124	25	275	147	99	29	0.05
Ebner <i>et al.</i> 2010 [25]	263	138	108	17	254	137	103	14	0.34
krivokuca <i>et al.</i> 2014 [14]	155	87	58	10	114	62	45	7	0.76
Menzel <i>et al.</i> 2004 [12]	302	158	114	30	475	275	170	30	0.59
Wang-Gohrke <i>et al.</i> 2002 [26]	552	282	221	49	543	300	203	40	0.49

N: Number, Arg/Arg: wild-type, Arg/Pro: Heterozygous, Pro/Pro: muted homozygous

Figures

Fig. 1 Flow diagram of the studies evaluated for meta-analysis

Figure 1

Flow diagram of the studies evaluated for meta-analysis

Fig. 2 Funnel plots of dominant (a), recessive (b) and additive (c) models precision by OR

Figure 2

Funnel plots of dominant (a), recessive (b) and additive (c) models precision by OR

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