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Association between the p53 polymorphisms and breast cancer risk: meta-analysis based on case–control study

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Abstract p53 is a tumor suppressor gene and plays an important role in the etiology of breast cancer. However, studies on the association between p53 polymorphisms and breast cancer risk have yielded conflicting results. We performed a meta-analysis to investigate the association between breast cancer and the p53 polymorphisms codon 72 (27,046 cases and 30,998 controls), IVS3 16 bp (3,332 cases and 3,700 controls) and IVS6+62A>G (8,787 cases and 9,869 controls) in different inheritance models. When all the eligible studies of codon 72 polymorphism were pooled into this meta-analysis, there was no evidence of significant association between breast cancer risk and p53 codon 72 polymorphism in any genetic model. However, in the stratified analysis for Indian population, significantly association was observed in additive model (OR = 0.62, 95% CI = 0.46–0.82, P value of heterogeneity test [P_h] = 0.153) and recessive model (OR = 0.70, 95% CI = 0.50–0.92, P_h = 0.463). IVS3 16 bp was significantly associated with breast cancer risk in a pooled 15 studies dataset (dominant model: OR = 1.14, 95% CI = 1.02–1.27, P_h = 0.30; recessive model: OR = 1.61, 95% CI = 1.21–2.25, P_h = 0.25; additive model: OR = 1.66, 95% CI = 1.24–2.21, P_h = 0.28). No significant association was found between IVS6+62A>G polymorphism and breast cancer risk in a total of 14 studies. In summary, these results indicate that IVS3 16 bp is likely an important genetic marker contributing to susceptibility of breast cancer, and codon 72 homozygous mutants may be associated with decreased breast cancer risk in Indian population.

Keywords TP53 · Polymorphism · Breast cancer · Meta-analysis

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Introduction

Breast cancer, a malignant proliferation of the epithelial cells that line the ducts or lobules of the breast, is the most common malignancy in women [1], accounting for approximately one-third of all cancers in women worldwide [2]. Although many risk factors for the development of breast cancer have been identified, such as the inherited genetic predisposition, the molecular mechanisms related to breast carcinogenesis remain under investigation [3, 4]. The disease seems to be the result of cumulative alterations of oncogenes and tumor suppressor genes that lead to clonal outgrowth of progressively malignant cells [5, 6].

Tumor suppressor gene p53 which located on 17p13 is one of the major markers of human tumor and one of the most commonly mutated genes in human cancer [7]. The p53 protein has a very important function in many physiological processes, such as cell cycle arrest, DNA repair, apoptosis, and gene transcription [8]. In addition to acquired mutations that alter its function in p53, there are many studies which have been identified in the p53 gene, the p53 codon 72 (rs1042522) polymorphism of exon 4 is a common single nucleotide polymorphism (SNP), where the variant encodes a proline (CCC) rather than an arginine (CGC) residue [9], it can affect p53 function. The two polymorphic variants have been indicated that their structure and biological properties were not the same [10].

Many studies have reported the role of p53 polymorphisms at codon 72 (rs1042522), IVS3 16 bp (rs17878362) and IVS6+62A>G (rs1625895) with breast cancer risk [15–68], but the results were inconclusive, some original studies thought that these polymorphisms were association with breast cancer risk, but others had different opinions. In addition, previous meta-analysis on p53 showed conflicting results. Hence, the correlation of this polymorphic gene remains unknown. In order to explore the association between p53 codon 72 (rs1042522), IVS3 16 bp (rs17878362) and IVS6+62A>G (rs1625895) polymorphisms with breast cancer risk, a Meta-analysis was conducted to summarize the data. Meta-analysis is a powerful tool for summarizing the different studies. It can not only overcome the problem of small size and inadequate statistical power of genetic studies of complex traits, but also provide more reliable results than a single case–control study.

Materials and methods

Search strategy and selection criteria

All the case–control studies were identified by a computerized literature search of the PubMed, EBSCO, and CGEMS database (prior to September 2010) using the following words and terms: "p53", "TP53", "polymorphism," and "breast," as well as their combinations. Only research articles were included and the language was not limited. The included studies have to meet the following criteria: (1) only the case–control studies and cohort studies were considered; (2) they were designed to evaluate the p53 codon 72, IVS3 16 bp (rs17878362) and IVS6+62A>G (rs1625895) polymorphisms and breast cancer risk, (3) the amount of published data was sufficient to allow estimation of an odds ratio (OR) with 95% confidence interval (CI); and (4) the distribution of genotypes among controls are in Hardy–Weinberg equilibrium ($P < 0.01$).

Data extraction

Information was carefully extracted from all eligible studies independently by two authors (He and Su) according to the inclusion criteria listed above. The following data were collected from each study: first author, year of publication, original country and ethnicity of the sample, source of controls, and genotype distribution. Disagreement was resolved by discussion between the two authors. If they could not reach a consensus, another author was consulted to resolve the dispute, and a final decision was made by two of this group of three authors. When a study reported results on different subpopulations according to ethnicity, we considered each subpopulation as a separate study in the meta-analysis.

Statistical analysis

The strength of association between p53 polymorphisms and breast cancer risk was assessed by Crude ORs with the corresponding 95% CIs. The pooled ORs were performed for an additive model (CC vs. YY), recessive model (CC vs. CY+YY) and a dominant model (CC+CY vs. YY). Heterogeneity among studies was checked by the Q test; the P value of more than 0.1 for the Q test indicates a lack of heterogeneity among studies, so the pooled OR was calculated by the fixed-effects model [69]. Otherwise, a random-effects model was used [70]. If heterogeneity was present we might use meta-regression analysis in exploring sources of heterogeneity [71]. In addition, subgroup analyses were conducted by ethnicity and resource of controls. Sensitivity analyses were performed to estimate the robustness of the summary estimate of alteration in breast cancer risk conferred by p53 codon 72 (rs1042522), IVS3 16 bp (rs17878362), and IVS6+62A>G (rs1625895) polymorphisms. Begg's funnel plots [72] and Egger's linear regression test [73] were used to assess publication bias. In the control group, Hardy–Weinberg equilibrium (HWE) was tested for using a goodness-of-fit chi-square test. All of the calculations were performed using STATA version 10.0 (STATA Corporation, College Station, TX).

Results

Study characteristics

Table 1 listed the main characteristics and genotype distribution of codon 72 polymorphism (rs1042522), with a total of 56 eligible studies met the inclusion criteria, including first author, published year, ethnicity, original country, source of controls, and genotype distribution. However, the study of Pharoah et al. [50] and the study of Samson et al. [51] were excluded because subjects had been included by Baynes et al. [38] and Rajkumar et al. [44]. The distribution of genotypes in the controls was consistent with Hardy–Weinberg equilibrium in all studies except for two studies ($P < 0.01$) [21, 65], these studies were excluded in this meta-analysis. Hence, leaving 52 eligible studies (27,046 cases and 30,998 controls) that had assessed the association between the codon 72 polymorphism and breast cancer risk.

Table 2 listed the main characteristics and genotype distribution of IVS3 16 bp polymorphism (rs17878362), with a total of 15 eligible studies (3,332 cases and 3,700 controls) for investigating IVS3 16 bp polymorphism and breast cancer risk.

Table 3 listed the main characteristics and genotype distribution of IVS6+62A>G polymorphism (rs1625895), with a total of 14 eligible studies (8,787 cases and 9,869 controls) for investigating VS6+62A>G polymorphism and breast cancer risk.

Meta-analysis results

Codon 72 polymorphism

Table 4 listed the main results of the meta-analysis of codon 72 polymorphism and breast cancer risk. When all the eligible studies were pooled into this meta-analysis of codon 72, there was no evidence of significant association between breast cancer risk and p53 codon 72 polymorphism in any genetic model (dominant model: odds ratio [OR] = 0.97, 95% confidence interval [CI] = 0.90–1.05, P value of heterogeneity test [P_h] < 0.001; recessive model: OR = 0.96, 95% CI = 0.88–1.06, $P_h = 0.009$; additive model: OR = 0.95, 95% CI = 0.85–1.07, $P_h < 0.001$). Significant between-study heterogeneity was detected in any genetic model. Hence, we performed the stratified analysis according to ethnicity, source of controls, and sample size. In the stratified analysis for India population, significantly decreased risk of breast cancer was observed in additive model (OR = 0.62, 95% CI = 0.46–0.82, $P = 0.001$, $P_h = 0.153$, Fig. 1) and recessive model (OR = 0.70, 95% CI = 0.50–0.92, $P_h = 0.463$, Fig. 2).

Previous codon 72 polymorphism

Three meta-analyses have been previously published for codon 72 polymorphism and breast cancer risk [11–14]. Table 4 listed the main results of meta-analysis of previous codon 72 polymorphism and breast cancer risk.

The study of Zhang et al. [11] had 39 studies, when all the eligible studies were pooled into the meta-analysis, significantly decreased risk of breast cancer was observed in dominant model (OR = 0.90, 95% CI: 0.82–0.99). In the stratified analysis by ethnicity, significantly decreased risk was also observed in European populations (dominant model: OR = 0.88, 95% CI: 0.80–0.98). In the stratified analysis by source of controls, they found that the variant genotypes were associated with a significantly decreased breast cancer risk in dominant model and additive model (dominant model: OR = 0.87. 95% CI: 0.78–0.97; homozygote comparison: OR = 0.88, 95% CI: 0.78–1.00).

The study of Hu et al. [12] had 37 studies, significantly decreased risk of breast cancer was found between Mediterranean and Northern European populations (recessive model: OR = 0.32, 95% CI: 0.24–0.44; additive model: OR = 0.35, 95% CI: 0.21–0.60). The data for this meta-analysis only included 375 cases and 389 controls from 6 studies between Mediterranean and Northern European populations.

The study of Ma et al. [13] had 21 studies, when all the eligible studies were pooled into the meta-analysis, significantly increased risk of breast cancer was observed in dominant model (OR = 1.179, 95% CI = 1.020–1.362). In the stratified analysis by source of controls, significantly increased risk was also observed by population-based study (dominant model: OR = 1.23, 95% CI = 1.05–1.43; recessive model: OR = 1.16, 95% CI = 1.01–1.33; additive model: OR = 1.28, 95% CI = 1.04–1.59).

The study of Francisco et al. [14] had 42 case–control studies reporting an association between the p53 codon 72 polymorphism and breast cancer. When all the eligible studies were pooled into the meta-analysis, no significant association of breast cancer risk was found in any genetic model. In the stratified analysis by source of country, significantly decreased risk was observed in Indian population (dominant model: OR = 0.75, 95% CI = 0.61–0.93; Arg/Arg vs. Pro/Pro: OR = 0.70, 95% CI = 0.53–0.91; recessive model: OR = 0.77, 95% CI = 0.61–0.97) in Indian population.

IVS3 16 bp polymorphism

Table 5 listed the main results of the meta-analysis of the IVS3 16 bp polymorphism and breast cancer risk. When all the eligible studies were pooled into the meta-analysis, significantly increased risks of breast cancer were observed

Table 1 Main characteristics and genotype distribution of codon 72 polymorphism (rs1042522)

First author	Year	Country	Ethnicity	SC	Genotype distribution						HWE
					Case			Control			
					CC	CG	GG	CC	CG	GG	
Kawajiri [15]	1993	Japan	Asian	PB	37	51	5	144	165	38	0.66
Sjalander [16]	1996	Sweden	Caucasian	PB	95	93	24	375	253	61	0.15
Weston [17]a	1997	USA	Caucasian	HB	32	27	6	72	42	3	0.55
Weston [17]b	1997	USA	African	HB	6	9	1	12	14	4	1.00
Weston [17]c	1997	USA	Hispanic	HB	3	8	7	10	16	12	0.63
Helland [18]	1998	USA	NR	NR	63	40	6	122	90	13	0.79
Gohrke [19]	1998	Germany	Caucasian	PB	56	46	5	167	117	21	0.99
Khaliq [20]	2000	Pakistani	Asian	PB	10	18	13	191	321	177	0.26
Papadakis [21]	2000	Greece	Caucasian	NR	34	10	12	12	41	6	0.00
Li [22]	2002	China	Asian	PB	11	11	6	10	26	14	0.94
Gohrke [23]	2002	German	Caucasian	PB	282	221	49	300	203	40	0.78
Buyru [24]	2003	Turkey	Caucasian	PB	64	39	12	21	43	12	0.43
Mabrouk [25]	2003	Tunisia	African	PB	18	9	3	19	26	4	0.49
Huang [26]	2003	Japan	Asian	HB	64	100	36	114	138	30	0.46
Katiyar [27]	2003	India	Asian	HB	20	51	6	9	24	8	0.54
Suspitsin [28]	2003	Russian	Caucasian	HB	284	203	42	207	159	27	0.89
Menzel [29]	2004	Czech	Caucasian	PB	275	170	30	158	114	30	0.29
Noma [30]	2004	Japan	Asian	PB	93	69	29	111	76	31	0.01
Mahasneh [31]	2004	Jordanian	Asian	PB	16	19	8	56	51	29	0.04
Tommiska [32]	2005	Finland	Caucasian	PB	825	617	109	403	278	52	0.91
Kalemi [33]	2005	UK	Caucasian	PB	26	13	3	10	32	9	0.19
Siddique [34]	2005	China	Asian	PB	36	38	20	107	120	38	0.89
Ohayon [35]	2005	Israel	Caucasian	HB	89	40	3	54	94	19	0.07
Damin [36]	2006	Brazil	Mixed	PB	64	48	6	70	111	21	0.06
Ma [37]	2006	China	Asian	PB	149	178	77	150	222	100	0.57
Baynes [38]	2007	UK	Caucasian	PB	1,107	768	148	1,177	854	166	0.81
Gochhait [39]	2007	India	Asian	NR	86	109	48	76	160	97	0.81
Khadang [40]	2007	Iran	Asian	HB	83	109	29	75	90	40	0.39
Schmidt [41]	2007	Finland	Caucasian	PB	4,499	3,228	618	3,661	2,677	511	0.78
Sprague [42]	2007	USA	Caucasian	PB	909	644	100	1,021	704	129	0.26
Zhang [43]	2007	China	Asian	PB	21	45	17	47	87	33	0.81
Rajkumar [44]	2007	India	Asian	NR	66	125	59	135	224	141	0.06
Cox [45]	2007	USA	Mixed	HB	804	569	104	1,255	838	131	0.85
Gaudet [46]	2007	USA	Mixed	PB	288	244	46	218	138	34	0.21
Closas [47]	2007	N and P	Caucasian	HB	1,368	1,021	196	1,774	1,249	228	0.92
Johnson [48]	2007	UK	Caucasian	HB	257	185	30	1,354	925	183	0.35
Franekova [49]	2007	Slovakia	Caucasian	HB	49	34	8	92	55	9	0.97
Akkiprik [52]	2008	Turkey	Caucasian	PB	25	50	20	46	49	12	0.98
Singh [53]	2008	India	Asian	HB	46	45	13	29	64	12	0.04
Lum [54]	2008	China	Asian	PB	105	200	88	29	38	13	0.99
Cavallone [55]	2008	France	Caucasian	PB	80	67	10	57	46	9	0.99
Costa [56]	2008	Portugal	Caucasian	HB	137	86	25	380	212	54	0.24
De [57]	2008	Italy	Caucasian	HB	185	150	15	207	131	14	0.48
Nordgard [58]	2008	Norway	Caucasian	PB	46	58	5	73	34	14	0.02
Henrırquez [59]	2009	Spain	Caucasian	PB	73	54	8	167	100	28	0.08

Table 1 continued

First author	Year	Country	Ethnicity	SC	Genotype distribution						HWE
					Case			Control			
					CC	CG	GG	CC	CG	GG	
Kazemi [60]	2009	Iran	Asian	HB	6	30	6	12	45	0	0.02
Evgeniy [61]	2009	Russian	Caucasian	PB	148	124	25	147	99	29	0.15
Aoki [62]	2009	Brazil	Mixed	PB	40	29	3	30	53	7	0.05
Song [63]	2009	China	Asian	PB	339	544	221	349	508	220	0.44
Anna [64]	2009	Sweden	Caucasian	PB	65	45	6	79	58	5	0.35
Hrstka [65]	2009	Czech	Caucasian	PB	62	15	40	55	8	45	0.00
Kara [66]	2010	Turkish	Caucasian	PB	105	84	14	72	80	17	0.74
Ebner [67]	2010	Germany	Caucasian	PB	138	108	17	137	103	14	0.63
Bisof [68]	2010	Croatia	Caucasian	PB	61	23	11	61	42	5	0.80

PB population-based study, *HB* hospital-based study, *NR* not reported, *HWE* Hardy–Weinberg equilibrium, *CC* indicates Wild-type, *CY* indicates heterozygote, *YY* indicates variant homozygote, *SC* source of controls, a–c: They were different case–control studies in one publication

Table 2 Main characteristics and genotype distribution of IVS3 16 bp polymorphism (rs17878362)

First author	Year	Country	Ethnicity	SC	Genotype distribution						HWE
					Case			Control			
					CC	CG	GG	CC	CG	CC	
Sjalander [16]	1996	Sweden	Caucasian	PB	162	46	4	529	142	18	0.09
Weston [17]a	1997	USA	Caucasian	HB	41	21	3	93	23	1	0.97
Weston [17]b	1997	USA	African	HB	4	12	0	13	15	2	0.65
Weston [17]c	1997	USA	Hispanic	HB	15	3	0	21	16	1	0.61
Gohrke [19]	1998	Germany	Caucasian	PB	370	173	20	391	145	13	0.99
Suspitsin [28]	2003	Russian	Caucasian	HB	408	108	13	187	56	6	0.78
Buyru [74]	2007	Turkey	Caucasian	PB	83	28	4	47	15	1	1.00
Gaudet [46]	2007	USA	Mixed	PB	404	157	17	272	108	10	0.98
Cavallone [55]	2008	France	Caucasian	PB	102	53	2	79	32	1	0.50
Costa [56]	2008	Portugal	Caucasian	HB	168	71	22	446	195	15	0.50
Akkiprik [52]	2008	Turkey	Caucasian	PB	59	35	3	61	43	3	0.36
De [57]	2008	Italy	Caucasian	HB	233	103	14	256	87	9	0.89
Hrstka [65]	2009	Czech	Caucasian	PB	81	32	4	81	24	3	0.79
Bisof [68]	2010	Croatia	Caucasian	PB	67	21	7	77	31	0	0.63

PB population-based study, *HB* hospital-based study, *HWE* Hardy–Weinberg equilibrium, *CC* indicates Wild-type, *CY* indicates heterozygote, *YY* indicates variant homozygote, *SC* source of controls

in any genetic model (dominant model: OR = 1.14, 95% CI = 1.02–1.27, $P = 0.017$, P value of heterogeneity test [P_h] = 0.30, Fig. 3; recessive model: OR = 1.61, 95% CI = 1.21–2.25, $P = 0.001$, $P_h = 0.25$, Fig. 4; additive model: OR = 1.66, 95% CI = 1.24–2.21, $P = 0.001$, $P_h = 0.28$, Fig. 5). Moreover, significant between-study heterogeneity was not detected in the meta-analysis of the IVS3 16 bp polymorphism and breast cancer under any genetic model.

IVS6+62A>G polymorphism

Table 6 listed the main results of the meta-analysis of the IVS6+62A>G polymorphism and breast cancer risk. When all the eligible studies were pooled into the meta-analysis, no significant association of breast cancer risk was found in any genetic model (dominant model: OR = 1.03, 95% CI = 0.91–1.18, $P = 0.82$, P value of heterogeneity test [P_h] = 0.009; recessive model: OR = 0.93, 95% CI = 0.76–1.14,

Table 3 Main characteristics and genotype distribution of IVS6+62A>G polymorphism (rs1625895)

First author	Year	Country	Ethnicity	SC	Genotype distribution						HWE
					Case			Control			
					CC	CG	GG	CC	CG	CC	
Sjalander [16]	1996	Sweden	Caucasian	PB	161	48	3	525	146	18	0.14
Weston [17]a	1997	USA	Caucasian	HB	43	20	2	95	22	0	0.80
Weston [17]b	1997	USA	African	HB	3	13	0	12	16	2	0.57
Weston [17]c	1997	USA	Hispanic	HB	16	2	0	23	13	2	1.00
Gohrke [19]	1998	Germany	Caucasian	PB	388	157	18	399	139	10	0.87
Suspitsin [28]	2003	Russian	Caucasian	HB	426	94	9	195	50	4	0.92
Buyru [74]	2007	Turkey	Caucasian	PB	107	7	1	56	6	1	0.25
Closas [47]	2007	N and P	Caucasian	HB	2,080	564	37	2,686	641	55	0.08
Sprague [42]	2007	USA	Caucasian	PB	1,254	359	35	1,358	438	50	0.12
Baynes [38]	2007	UK	Caucasian	PB	1,545	449	48	1,622	520	55	0.22
Gaudet [46]	2007	USA	Mixed	PB	412	152	14	282	99	9	0.99
Singh [53]	2008	India	Asian	HB	80	20	4	74	28	3	1.00
Akkiprik [52]	2008	Turkey	Caucasian	PB	51	39	9	61	38	8	0.83
Hrstka [65]	2009	Czech	Caucasian	PB	76	39	2	83	23	2	0.98

$P = 0.49$, $P_h = 0.85$; additive model: OR = 0.93, 95% CI = 0.76–1.14, $P = 0.51$, $P_h = 0.80$). Moreover, significant between-study heterogeneity was not detected in the meta-analysis of the IVS6+62A>G polymorphism and breast cancer under any genetic model, except for dominant model ($P = 0.009$ for heterogeneity).

Next, we performed stratified analysis by source of controls and ethnicity, in stratified subgroup meta-analysis, the IVS6+62A>G polymorphism was not found to be associated with breast cancer risk too.

Sensitive analysis

We tested the inclusion criteria of this meta-analysis by a sensitivity analysis. Sensitivity analysis were conducted to determine whether modification of the inclusion criteria of this meta-analysis affected the results, A single study involved in the meta–analysis was deleted each time to reflect the influence of individual data set to the pooled ORs, and the corresponding pooled ORs were not essentially altered (data not shown), indicating that our results were statistically robust.

Publication bias

Both Begg's funnel plot and Egger's test were performed to access the publication bias of this meta-analysis. Begg's funnel plots did not reveal any evidence of obvious asymmetry in any genetic model in the overall meta-analysis (Figures not shown). The Egger's test results suggested no evidence of publication bias in the meta-analysis of codon 72 ($P = 0.259$ for dominant model, $P = 0.514$ for recessive model, $P = 0.328$ for additive model); IVS3 16 bp ($P = 0.869$ for dominant model, $P = 0.694$ for recessive model, $P = 0.744$ for additive model) and IVS6+62A>G ($P = 0.663$ for dominant model, $P = 0.566$ for recessive model, $P = 0.426$ for additive model), indicating that our results were statistically robust.

Discussion

Many studies have reported the role of p53 polymorphisms at codon 72 (rs1042522), IVS3 16 bp (rs17878362) and IVS6+62A>G (rs1625895) with breast cancer risk [15–68], but the results were inconclusive, some original studies thought that these polymorphisms were associated with breast cancer risk, but other original studies thought no association with breast cancer risk. In addition, previous meta-analysis on codon 72 polymorphism showed conflicting results. Hence, a meta-analysis was conducted to explore the association between p53 codon 72, IVS3 16 bp and IVS6+62A>G polymorphisms and breast cancer risk.

Our present meta-analysis, which included 27,046 cases and 30,998 cases from 52 studies, explored the association between the p53 codon 72 polymorphism and breast cancer risk. The results indicated that codon 72 polymorphism may be not associated with breast cancer risk in Caucasian population. In the stratified analysis for Indian population, significantly decreased risk of breast cancer was observed in additive model (OR = 0.62, 95% CI = 0.46–0.82, $P = 0.001$, $P_h = 0.153$) and recessive model (OR = 0.70,

Table 4 Description of current and published meta-analysis for select codon 72 polymorphism and breast cancer

Study	*N*	Case/control	Recessive		Dominant		Additive	
			OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
Overall								
Zhang et al. [11]	39	26,041/29,679	0.95 (0.87–1.04)[a]	0.032	0.90 (0.82–0.99)[a]	0.000	0.92 (0.82–1.04)[a]	0.000
Hu et al. [12]	37	23,567/25,995	0.98 (0.89–1.09)[a]	0.01	0.96 (0.88–1.03)[a]	0.000	0.96 (0.85–1.08)[a]	0.000
Ma et al. [13]	21	22,515/22,388	1.15 (0.98–1.34)[a]	0.008	1.18 (1.02–1.36)[a]	0.000	1.25 (0.99–1.55)[a]	0.000
Francisco [14]	42	23,429/28,000	0.97 (0.87–1.08)	NA	0.95 (0.88–1.03)	NA	0.97 (0.87–1.08)	NA
Present	52	27,046/30,998	0.96 (0.88–1.06)[a]	0.009	0.97 (0.90–1.05)[a]	0.000	0.95 (0.85–1.07)[a]	0.000
Caucasian								
Zhang et al. [11]	29	NA	0.96 (0.87–1.06[a]	0.03	0.88 (0.80–0.98)[a]	0.000	0.92 (0.81–1.05)[a]	0.000
Hu et al. [12]	20	17,419/18,173	1.01 (0.93–1.09)	0.46	1.01 (0.97–1.06)	0.19	1.01 (0.93–1.10)	0.25
Ma et al. [13]	NA	NA	1.10 (0.93–1.32)	0.06	1.11 (0.92–1.34)[a]	0.000	1.16 (0.89–1.51)[a]	0.000
Francisco [14]	18	15,791/18,308	1.06 (0.98–1.16)	NA	1.02 (0.98–1.07)[a]	NA	1.07 (0.98–1.16)	NA
Present	27	21,017/22,726	0.97 (0.84–1.12[a]	0.049	1.00 (0.90–1.10)[a]	0.000	0.97 (0.84–1.12)[a]	0.000
Asian								
Zhang et al. [11]	9	NA	0.93 (0.70–1.23)	0.059	1.01 (0.82–1.25)	0.065	0.92 (0.65–1.31)	0.013
Hu et al. [12]	11	2,270/2,848	0.91 (0.71–1.19)[a]	0.01	0.94 (0.77–1.16)[a]	0.004	0.87 (0.73–1.03)[a]	0.000
Ma et al. [13]	NA	NA	1.16 (0.70–1.91)[a]	0.002	1.11 (0.76–1.61)[a]	0.007	1.21 (0.63–2.32)[a]	0.000
Francisco [14]	5	1,281/1,399	1.15 (0.91–1.46)	NA	1.07 (0.90–1.26)	NA	1.14 (0.91–1.41)	NA
Present	17	3,611/5,024	0.95 (0.79–1.15)[a]	0.01	0.98 (0.84–1.14)	0.01	0.94 (0.74–1.20)[a]	0.001
India								
Francisco [14]	5	715/1,668	0.70 (0.53–0.91)[a]	NA	0.75 (0.61–0.93)[a]	NA	0.77 (0.61–0.97)[a]	NA
Present	4	674/979	0.70 (0.50–0.92)	0.463	0.68 (0.45–1.03)[a]	0.037	0.62 (0.46–0.82)	0.153
PB								
Zhang et al. [11]	30	NA	0.94 (0.87–1.02)[a]	0.000	0.87 (0.78–0.97)[a]	0.000	0.88 (0.77–1.00)[a]	0.000
Ma et al. [13]	NA	NA	1.16 (1.01–1.33)[a]	0.082	1.23 (1.05–1.43)[a]	0.000	1.28 (1.04–1.59)[a]	0.000
Present	33	19,817/19,414	0.96 (0.90–1.03)	0.27	0.98 (0.89–1.08)[a]	0.000	0.94 (0.83–1.07)[a]	0.008
HB								
Zhang et al. [11]	7	NA	1.12 (0.78–1.62)	0.058	0.97 (0.66–1.42)[a]	0.000	0.95 (0.66–1.37)[a]	0.000
Ma et al. [13]	NA	NA	1.15 (0.98–1.34)[a]	0.007	0.88 (0.57–1.35)	0.25	1.25 (0.99–1.55)[a]	0.004
Present	16	7,334/11,057	1.05 (0.85–1.30)[a]	0.003	0.99 (0.86–1.14)[a]	0.000	1.05 (0.83–1.34)[a]	0.000
>500 subject								
Zhang et al. [11]	18	NA	0.97 (0.91–1.03)	0.302	1.02 (0.96–1.08)[a]	0.023	0.99 (0.92–1.06)	0.078
Present	21	23,652/26,485	0.98 (0.92–1.04)	0.370	1.03 (0.98–1.10[a]	0.016	0.99 (0.93–1.06)[a]	0.06
>500 subject for caucasian population								
Zhang et al. [11]	17	NA	0.97 (0.91–1.04)	0.263	1.02 (0.97–1.09)[a]	0.033	1.00 (0.93–1.07)	0.086
Present	14	19,555/20,800	0.99 (0.92–1.07)	0.69	1.02 (0.98–1.06)	0.203	1.00 (0.93–1.09)	0.47
>500 subject for Asian population								
Present	5	2,042/3,071	0.87 (0.76–1.01)	0.167	0.88 (0.67–1.14)[a]	0.011	0.81 (0.59–1.12)[a]	0.017

P_h *P* values for heterogeneity from *Q* test, *NA* not available, *N* number of study

[a] Random-effect model was used when $P_h < 0.05$; otherwise, fixed-effects model was used

95% CI = 0.50–0.92, $P_h = 0.463$). The result indicated that codon 72 polymorphism may be associated with breast cancer risk, but there are only four studies in Indian population, to determine whether codon 72 polymorphism be applied to clinical genotyping for risk assessment still require large scale breast cancer case–controls researches in Indian population.

In this meta-analysis, significant association of the IVS3 16 bp polymorphism and breast cancer risk was found (dominant model: OR = 1.14, 95% CI = 1.02–1.27, $P = 0.017$, *P* value of heterogeneity test [P_h] = 0.30; recessive model: OR = 1.61, 95% CI = 1.21–2.25, $P = 0.001$, $P_h = 0.25$; additive model: OR = 1.66, 95% CI = 1.24–2.21, $P = 0.001$, $P_h = 0.28$). The result indicated that IVS3 16 bp

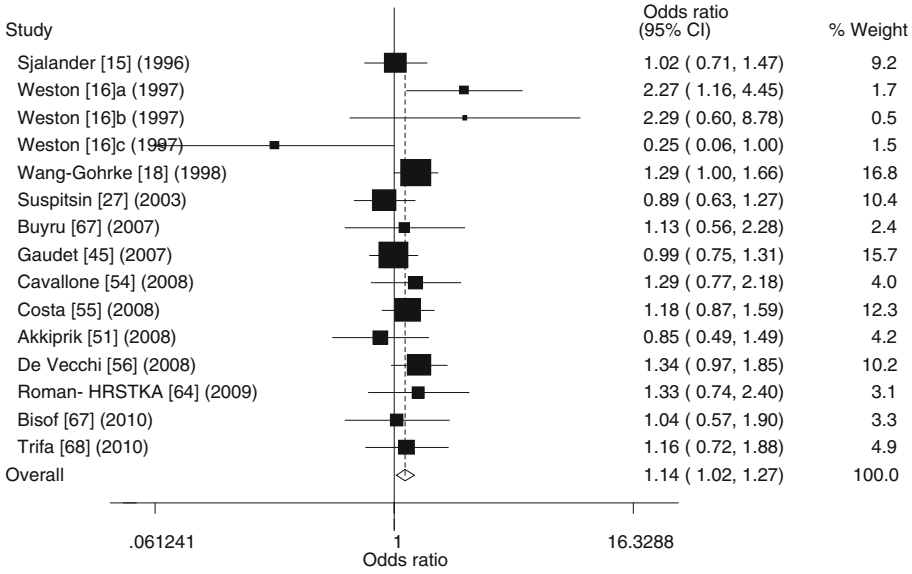

Fig. 1 Meta-analysis of OR for TP53 codon 72 polymorphism associated with breast cancer risk (additive model)

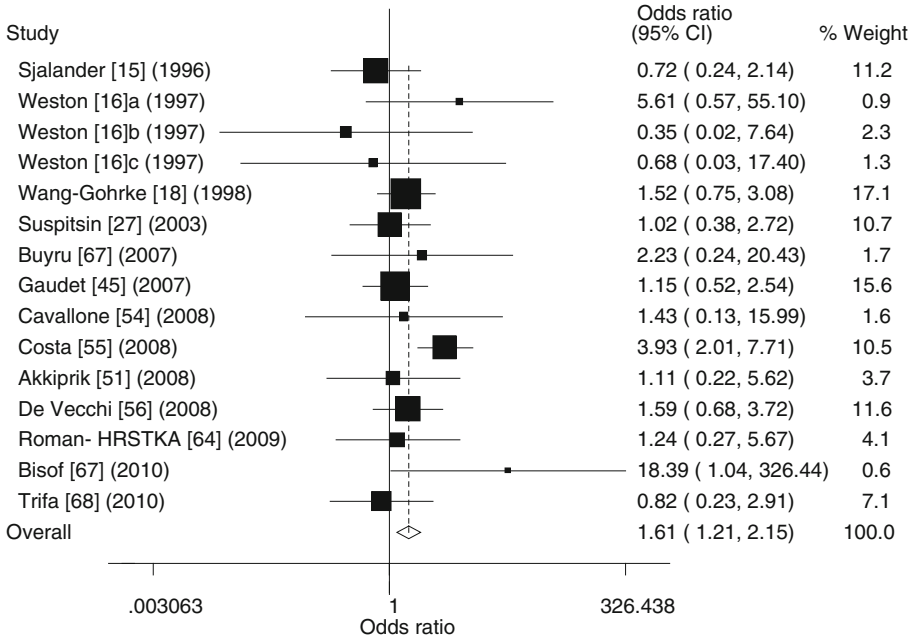

Fig. 2 Meta-analysis of OR for TP53 codon 72 polymorphism associated with breast cancer risk (recessive model)

Table 5 Results of the meta-analysis for IVS3 16 bp and breast cancer risk

Analysis	Case/control	Recessive		Dominant		Additive	
		OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
Overall	3,332/3,700	1.61 (1.21–2.15)	0.25	1.14 (1.02–1.27)	0.30	1.66 (1.24–2.21)	0.28

P a significant association was detected, P_h *P* values for heterogeneity from *Q* test, *CC* indicates Wild-type, *CY* indicates heterozygote, *YY* indicates variant homozygote

polymorphism may increase risk of developing breast cancer. To determine whether this marker should be applied to clinical genotyping for risk assessment still require large scale breast cancer case–control researches.

Meanwhile, no significant association of the IVS6+62A>G polymorphism and breast cancer risk was found. Hence, IVS6+62A>G may have no strong association with breast cancer risk, at least in our meta-analysis.

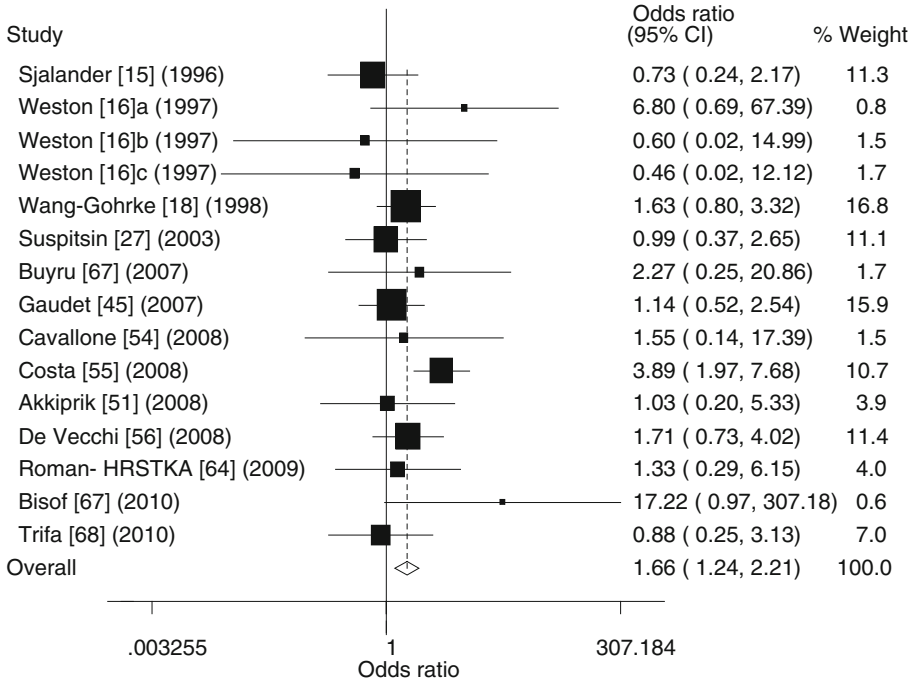

Fig. 3 Meta-analysis of Ors for TP53 16 bp polymorphism in intro 3 associated with breast cancer risk (dominant model)

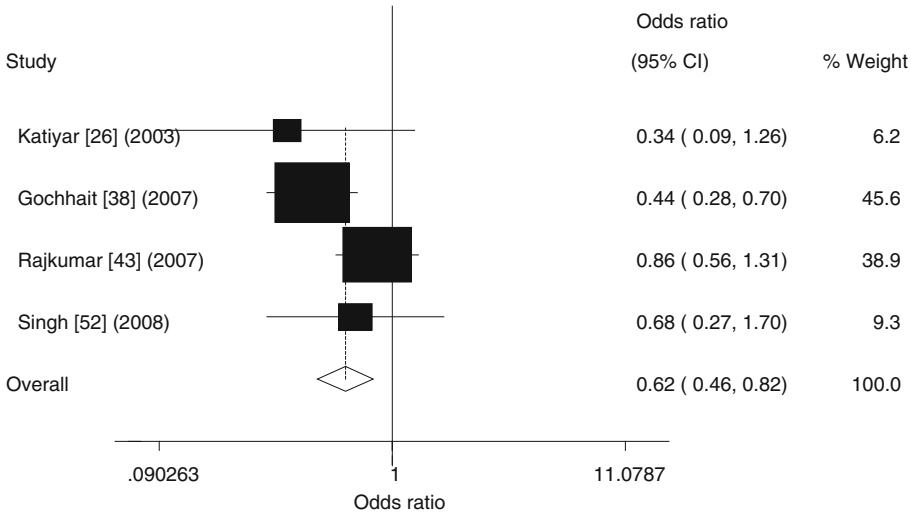

Fig. 4 Meta-analysis of Ors for TP53 16 bp polymorphism in intro 3 associated with breast cancer risk (recessive model)

Previous meta-analysis on p53 codon 72 showed conflicting results. We have read with great interest the article "No significant association between the p53 codon 72 polymorphism and breast cancer risk: a meta-analysis of 21 studies involving 24,063 subjects" Published online on May 23, 2010 issue of "Breast Cancer Research and Treatment" [13]. The study of Ma [13] have 21 case–control studies, his conclusion indicate that it provided strong evidence that the P53 codon 72 polymorphism is not association with the risk of developing breast cancer. Ma et al. [13] concluded that no significant association was found between the P53 codon 72 polymorphism and breast cancer risk when all the eligible studies were pooled into the meta-analysis, but significant risk of breast cancer was observed in dominant model (OR = 1.179, 95% CI = 1.020–1.362). Similarly, Ma et al. [13] demonstrated that no significant association was observed for any of the genetic models in the stratified analysis by source of controls. But in the stratified analysis by source of controls, significant increased risks were observed by source of controls (dominant model: OR = 1.23, 95% CI = 1.05–1.43; recessive model: OR = 1.16, 95% CI = 1.01–1.33; additive model: OR = 1.28, 95% CI = 1.04–1.59). Hence, the ongoing uncertainty still existed and the conclusion by Ma et al. [13] was not entirely credible. In addition, several sizeable eligible studies have not been included in this meta-analysis, we thought that these studies satisfied the search criteria. Importantly, the data reported by Ma et al. [13] for the study

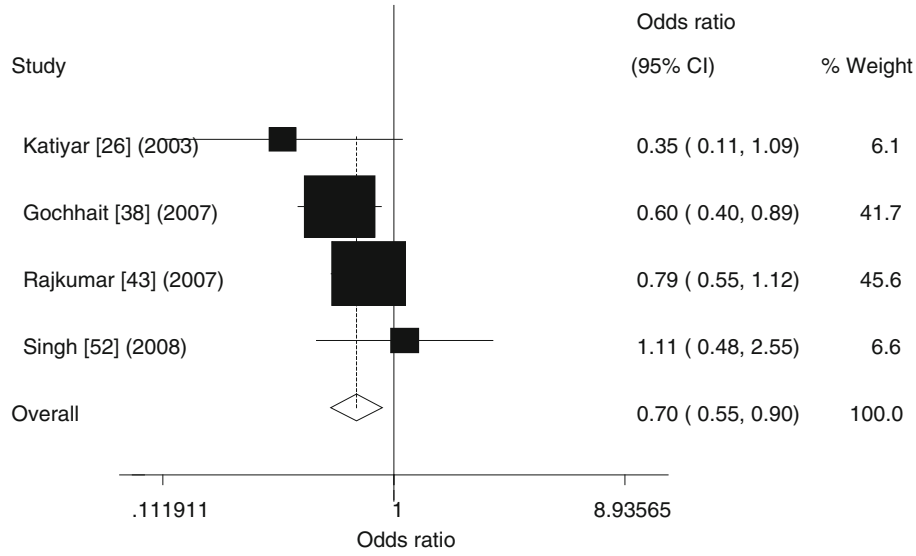

Fig. 5 Meta-analysis of OR for TP53 16 bp polymorphism in intro 3 associated with breast cancer risk (additive model)

Table 6 Results of the meta-analysis for IVS6+62A>G and breast cancer risk

Analysis	Case/control	Recessive		Dominant		Additive	
		OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
Overall ethnicity	8,787/9,869	0.93 (0.76–1.14)	0.85	1.03 (0.91–1.18)[a]	0.009	0.93 (0.76–1.14)	0.80
Caucasian	8,071/9,306	0.93 (0.75–1.15)	0.65	1.01 (0.94–1.08)	0.01	0.93 (0.75–1.15)	0.50
Source of controls							
PB	5,374/5,948	0.94 (0.74–1.20)	0.71	0.96 (0.88–1.05)	0.117	0.94 (0.73–1.19)	0.62
HB	3,413/3,921	0.91 (0.63–1.32)	0.65	0.93 (0.65–1.35)	0.02	0.93 (0.65–1.35)	0.65
>500 subject							
Overall	8,253/9,301	0.91 (0.74–1.12)	0.63	0.99 (0.93–1.07)	0.11	0.91 (0.73–1.12)	0.58

[a] Random-effect model was used when $P_h < 0.05$; otherwise, fixed-effects model was used

by Schimit et al. [41] do not seem in line with the data provided by Schimit et al. [41] in their original publication. The numbers reported by Ma et al. [13] for Arg/Arg, Arg/Pro, Pro/Pro, in cases and controls, are 2797-2008-386 and 2024-1523-287, respectively. Interestingly enough, after carefully studying the data presented by Schimit et al. [41], the frequencies that we have retrieved on the 8,345 cases and 6,849 controls were 4499-3228-618 and 3661-2677-511, respectively. The data reported by Ma et al. [13] for the study by Sjalander et al. [16] do not seem in line with the data provided by Sjalander et al. [16] in their original publication too. The numbers reported by Ma et al. [13] for Arg/Arg, Arg/Pro, Pro/Pro, in cases and controls, are 24-93-95 and 61-253-375, respectively. Interestingly enough, after carefully studying the data presented by Sjalander et al. [16], the frequencies that we have retrieved on the 212 cases and 689 controls were 95-93-24 and 375-253-61, respectively. The data reported by Ma et al. [13] for the study by Sprague et al. [42] do not seem in line with the data provided by Sprague et al. [42] in their original publication too. The numbers reported by Ma et al. [13] for Arg/Arg, Arg/Pro, Pro/Pro, in cases and controls, are 823-570-89 and 705-490-83, respectively. Interestingly enough, after carefully studying the data presented by Sprague et al. [42], the frequencies that we have retrieved on the 1,653 cases and 1,854 controls were 909-644-100 and 1021-704-129, respectively. The data reported by Ma et al. [13] for the study by Weston et al. [17] do not seem in line with the data provided by Weston et al. [17] in their original publication too. The numbers reported by Ma et al. [13] for Arg/Arg, Arg/Pro, Pro/Pro, in cases and controls, are 6-27-32 and 3-42-72, respectively, in Caucasian. Interestingly enough, after carefully studying the data presented by Weston et al. [17], the frequencies that we have retrieved on the 65 cases and 117 controls were 32-27-6 and 72-42-3 in Caucasian, respectively.

Secondly, we have also read great interest the recent meta-analysis by Zhang et al. [11], the study of Zhang [11] have 39 case–control studies, the results suggested that p53 codon 72 polymorphism may contribute to susceptibility to breast cancer, especially in Europeans. Zhang et al. [11] concluded that significant association was found between

the TP53 codon 72 polymorphism and breast cancer risk in the stratified analysis by ethnicity (Arg/pro vs. Arg/Arg: OR 0.89, 95% CI 0.80–0.99; dominant model: OR 0.88, 95% CI 0.80–0.98) and source of controls (Arg/pro vs. Arg/Arg: OR 0.88, 95% CI 0.78–0.98; dominant model: OR 0.87, 95% CI 0.78–0.97). But *P* value of *Q* test for heterogeneity test <0.001, when heterogeneity was very big, the results cannot be concluded that p53 codon 72 polymorphism may contribute to susceptibility to breast cancer, especially in Europeans. Hence, the ongoing uncertainty still existed and the conclusion by Zhang et al. [11] was not entirely credible. In addition, the study of by Baynes et al. [38] and the study by Pharoah et al. [50] essentially represent the same study, two studies by Buyru et al. [24, 74] have been included in this meta-analysis; however, careful inspection of both studies reveals that the same cases hace been included in them. Hence, incorporating one of the two studies by Buyru et al. might seem more appropriate. Importantly, several sizeable eligible studies have not been included in Zhang et al. [11], we thought that these studies satisfied the search criteria.

Thirdly, we have also read with great interest the recent meta-analysis by Hu et al. [12], the study of Hu et al. [12] had 37 case–control studies, the results suggest that codon 72 had a potential role in association with breast cancer risk within certain populations or regions. Significantly decreased risk was observed by source of Ethnicity (dominant model: OR = 0.32, 95% CI = 0.24–0.44; Pro/Pro vs. Arg/Arg: OR = 0.35, 95% CI = 0.21–0.60) in the Mediterranean studies. In the Mediterranean was Caucasian, in addition, all eligible study was small sample in the Mediterranean. Hence, the ongoing uncertainty still existed and the conclusion by Hu et al. [12] was not entirely credible.

Last, we have also read with great interest the recent meta-analysis by Francisco et al. [14], the study of Francisco et al. [14] had 42 case–control studies reporting an association between the p53 codon 72 polymorphism and breast cancer. Significantly decreased risk was observed in Indian population (dominant model: OR = 0.75, 95% CI = 0.61–0.93; Arg/Arg vs. Pro/Pro: OR = 0.70, 95% CI = 0.53–0.91; recessive model: OR = 0.77, 95% CI = 0.61–0.97) in Indian population. The study of Francisco et al. [14] had only five case–control studies in Indian population, which include 715 cases and 1,668 controls. However, in our present meta-analysis, which including four case–control studies in Indian population, significantly decreased risk was only observed in additive model and recessive model. Sample size was not large in our present meta-analysis and Francisco et al. [14], hence, the results should be interpreted with caution. To determine whether codon 72 polymorphism be applied to clinical genotyping for risk assessment still require large scale breast cancer case–controls researches in Indian population.

However, there are several limitations in this meta-analysis. Our results should be interpreted with caution. First, the controls were not uniformly defined. Although all the controls were healthy populations, most of them were common populations, some controls were Population-based; other controls were hospital-based. Hence, non–differential misclassification bias is possible. Second, in the subgroup analysis may have had insufficient statistical power to check an association, Third, we were also unable to examine the interactions among gene–environment, lacking of the original data of the included studies limited our further evaluation of potential interactions, which may be an important component of the association between p53 codon 72 polymorphism and environment and breast cancer risk. Four, it was much difficult to get the all articles published in various language. We only included the studies published in English and Chinese. Last, our results were based on unadjusted published estimates. Because of data limitations, we were unable to adjust them such as age, smoking, alcohol consumption et al.

Overall, our results indicated that IVS3 16 bp polymorphism may increase risk of developing breast cancer; and codon 72 homozygous mutants may be associated with decreased breast cancer risk in India population.

References

1. Berns EM, van Staveren IL, Look MP, Smid M, Klijn JGM, Foekens JA (1998) Mutations in residues of TP53 that directly contact DNA predict poor outcome in human primary breast cancer. Br J Cancer 77:1130–1136
2. Parkin DM, Bray F, Ferlay J et al (2001) Estimating the world cancer burden: Globocan 2000. Int J Cancer 94:153–156
3. Veronesi U, Boyle P, Golsdhirsch A, Orecchia R, Viale G (2005) Breast cancer. Lancet 365:1727–1741
4. Yager JD, Davidson NE (2006) Mechanism of disease: estrogen carcinogenesis in breast cancer. N Engl J Med 354:270–282
5. Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell 100:57–70
6. Dumitrescu RG, Cotarla I (2005) Understanding breast cancer risk—where do we stand in 2005? J Cell Mol Med 9:208–221
7. Hollstein M, Sidransky D, Vogelstein B et al (1991) p53 mutations in human cancers. Science 253:49–53
8. Oren M (2003) Decision making by p53: life, death and cancer. Cell Death 10:431–442
9. Denehower LA (2005) p53 guardian and suppressor of longevity? Exp Gerontol 40:7–9
10. Dumont P, Leu JI, Della Pietra ACIII et al (2003) The codon 72 polymorphic variants of p53 have markedly different apoptotic potential. Nat Genet 33:357–365
11. Zhang Z, Wang M, Wu D, Wang M, Tong N, Tian Y, Zhang Z (2010) P53 codon 72 polymorphism contributes to breast cancer risk: a meta-analysis based on 39 case–control studies. Breast Cancer Res Treat 120(2):509–517
12. Hu Z, Li X, Yuan R, Ring BZ, Su L (2010) Three common TP53 polymorphisms in susceptibility to breast cancer, evidence from meta-analysis. Breast Cancer Res Treat 120(3):705–714

13. Ma Y, Yang J, Liu Z, Zhang P, Yang Z, Wang Y, Qin H (2011) No significant association between the TP53 codon 72 polymorphism and breast cancer risk: a meta-analysis of 21 studies involving 24,063 subjects. Breast Cancer Res Treat 125(1):201–205
14. Francisco G, Menezes PR, Eluf-Neto J, Chammas R (2010) Arg72Pro *TP53* polymorphism and cancer susceptibility: a comprehensive meta-analysis of 302 case-control studies. Int J Cancer. doi:10.1002/ijc.25710
15. Kawajiri K, Nakachi K, Imai K, Watanabe J, Hayashi S (1993) Germ line polymorphisms of p53 and CYP1A1 genes involved in human lung cancer. Carcinogenesis 14:1085–1089
16. Sjalander A, Birgander R, Hallmans G, Cajander S, Lenner P, Athlin L, Beckman G, Beckman L (1996) p53 polymorphisms and haplotypes in breast cancer. Carcinogenesis 17:1313–1316
17. Weston A, Pan CF, Ksieski HB, Wallenstein S, Berkowitz GS, Tartter PI, Bleiweiss IJ, Brower ST, Senie RT, Wolff MS (1997) p53 haplotype determination in breast cancer. Cancer Epidemiol Biomarkers Prev 6:105–112
18. Helland A, Langerod A, Johnsen H, Olsen AO, Skovlund E, Borresen-Dale AL (1998) p53 polymorphism and risk of cervical cancer. Nature 396:530–531
19. Wang-Gohrke S, Rebbeck TR, Besenfelder W et al (1998) p53 germline polymorphisms are associated with an increased risk for breast cancer in German women. Anticancer Res 18:2095–2099
20. Khaliq S, Hameed A, Khaliq T et al (2000) P53 mutations, polymorphisms, and haplotypes in Pakistani ethnic groups and breast cancer patients. Genet Test 4:23–29
21. Papadakis EN, Dokianakis DN, Spandidos DA (2000) p53 codon 72 polymorphism as a risk factor in the development of breast cancer. Mol Cell Biol Res Commun 3:389–392
22. Li T, Lu ZM, Guo M, Wu QJ, Chen KN, Xing HP, Mei Q, Ke Y (2002) p53 codon 72 polymorphism (C/G) and the risk of human papillomavirus-associated carcinomas in China. Cancer 95: 2571–2576
23. Wang-Gohrke S, Becher H, Kreienberg R, Runnebaum IB, Chang-Claude J (2003) Intron 3 16 bp duplication polymorphism of p53 is associated with an increased risk for breast cancer by the age of 50 years. Pharmacogenetics 12:269–272
24. Buyru N, Tigli H, Dalay N (2003) P53 codon 72 polymorphism in breast cancer. Oncol Rep 10:711–714
25. Mabrouk I, Baccouche S, El-Abed R, Mokdad-Gargouri R, Mosbah A, Saïd S, Daoud J, Frikha M, Jlidi R, Gargouri A (2003) No evidence of correlation between p53 codon 72 polymorphism and risk of bladder or breast carcinoma in Tunisian patients. Ann N Y Acad Sci 1010:764–770
26. Huang XE, Hamajima N, Katsuda N, Matsuo K, Hirose K, Mizutani M, Iwata H, Miura S, Xiang J, Tokudome S, Tajima K (2003) Association of p53 codon Arg72Pro and p73 G4C14-to-A4T14 at exon 2 genetic polymorphisms with the risk of Japanese breast cancer. Breast Cancer 10:307–311
27. Katiyar S, Thelma BK, Murthy NS, Hedau S, Jain N, Gopalkrishna V, Husain SA, Das BC (2003) Polymorphism of the p53 codon 72 Arg/Pro and the risk of HPV type 16/18-associated cervical and oral cancer in India. Mol Cell Biochem 252:117–124
28. Suspitsin EN, Buslov KG, Grigoriev MY, Ishutkina JG, Ulibina JM, Gorodinskaya VM, Pozharisski KM, Berstein LM, Hanson KP, Togo AV, Imyanitov EN (2003) Evidence against involvement of P53 polymorphism in breast cancer predisposition. Int J Cancer 103:431–433
29. Menzel HJ, Sarmanova J, Soucek P, Berberich R, Grünewald K, Haun M, Kraft HG (2004) Association of NQO1 polymorphism with spontaneous breast cancer in two independent populations. Br J Cancer 90:1989–1994
30. Noma C, Miyoshi Y, Taguchi T, Tamaki Y, Noguchi S (2004) Association of p53 genetic polymorphism (Arg72Pro) with estrogen receptor positive breast cancer risk in Japanese women. Cancer Lett 210:197–203
31. Mahasneh AA, Abdel-Hafiz SS (2004) Polymorphism of p53 gene in Jordanian population and possible associations with breast cancer and lung adenocarcinoma. Saudi Med J 25:1568–1573
32. Tommiska J, Eerola H, Heinonen M, Salonen L, Kaare M, Tallila J, Ristimäki A, von Smitten K, Aittomäki K, Heikkilä P, Blomqvist C, Nevanlinna H (2005) Breast cancer patients with p53 Pro72 homozygous genotype have a poorer survival. Clin Cancer Res 11:5098–5103
33. Kalemi TG, Lambropoulos AF, Gueorguiev M, Chrisafi S, Papazisis KT, Kotsis A (2005) The association of p53 mutations and p53 codon 72, Her 2 codon 655 and MTHFR C677T polymorphisms with breast cancer in Northern Greece. Cancer Lett 222:57–65
34. Siddique MM, Balram C, Fiszer-Maliszewska L, Aggarwal A, Tan A, Tan P, Soo KC, Sabapathy K (2005) Evidence for selective expression of the p53 codon 72 polymorphs: implications in cancer development. Cancer Epidemiol Biomarkers Prev 14:2245–2252
35. Ohayon T, Gershoni-Baruch R, Papa MZ, Distelman Menachem T, Eisenberg Barzilai S, Friedman E (2005) The R72P P53 mutation is associated with familial breast cancer in Jewish women. Br J Cancer 92:1144–1148
36. Damin AP, Frazzon AP, Damin DC, Roehe A, Hermes V, Zettler C, Alexandre CO (2006) Evidence for an association of TP53 codon 72 polymorphism with breast cancer risk. Cancer Detect Prev 30:523–529
37. Ma H, Hu Z, Zhai X, Wang S, Wang X, Qin J, Chen W, Jin G, Liu J, Gao J, Wang X, Wei Q, Shen H (2006) Joint effects of single nucleotide polymorphisms in P53BP1 and p53 on breast cancer risk in a Chinese population. Carcinogenesis 27:766–771
38. Baynes C, Healey CS, Pooley KA, Scollen S, Luben RN, Thompson DJ, Pharoah PD, Easton DF, Ponder BA, Dunning AM (2007) SEARCH breast cancer study: common variants in the ATM, BRCA1, BRCA2, CHEK2 and TP53 cancer susceptibility genes are unlikely to increase breast cancer risk. Breast Cancer Res 9(2):R27
39. Gochhait S, Bukhari SI, Bairwa N, Vadhera S, Darvishi K, Raish M, Gupta P, Husain SA, Bamezai RN (2007) Implication of BRCA2–26G>A 5′ untranslated region polymorphism in susceptibility to sporadic breast cancer and its modulation by p53 codon 72 Arg>Pro polymorphism. Breast Cancer Res 9:R71
40. Khadang B, Fattahi MJ, Talei A, Dehaghani AS, Ghaderi A (2007) Polymorphism of TP53 codon 72 showed no association with breast cancer in Iranian women. Cancer Genet Cytogenet 173:38–42
41. Schmidt MK, Reincke S, Broeks A, Braaf LM, Hogervorst FB, Tollenaar RA, Johnson N, Fletcher O, Peto J, Tommiska J, Blomqvist C, Nevanlinna HA, Healey CS, Dunning AM, Pharoah PD, Easton DF, Dörk T, Van't Veer LJ (2007) Breast cancer association consortium: do MDM2 SNP309 and TP53 R72P interact in breast cancer susceptibility? A large pooled series from the breast cancer association consortium. Cancer Res 67:9584–9590
42. Sprague BL, Trentham-Dietz A, Garcia-Closas M, Newcomb PA, Titus-Ernstoff L, Hampton JM, Chanock SJ, Haines JL, Egan KM (2007) Genetic variation in TP53 and risk of breast cancer in a population-based case control study. Carcinogenesis 28:1680–1686
43. Zhang W, Jin MJ, Chen K (2007) Association of p53 polymorphisms and its haplotypes with susceptibility of breast cancer. Zhejiang Da Xue Xue Bao Yi Xue Ban 36:561–566
44. Rajkumar T, Samson M, Rama R, Sridevi V, Mahji U, Swaminathan R, Nancy N (2008) TGFb1 (Leu10Pro), p53 (Arg72Pro) can predict for increased risk for breast cancer in south Indian women and TGFb1 Pro (Leu10Pro) allele predicts response to

neo-adjuvant chemo-radiotherapy. Breast Cancer Res Treat 112:81–87
45. Cox DG, Deer D, Guo Q, Tworoger SS, Hankinson SE, Hunter DJ, De Vivo I (2007) The p53 Arg72Pro and MDM2-309 polymorphisms and risk of breast cancer in the nurses' health studies. Cancer Causes Control 18:621–625
46. Gaudet MM, Gammon MD, Bensen JT, Sagiv SK, Shantakumar S, Teitelbaum SL, Eng SM, Neugut AI, Santella RM (2008) Genetic variation of TP53, polycyclic aromatic hydrocarbonrelated exposures, and breast cancer risk among women on Long Island, New York. Breast Cancer Res Treat 108:93–99
47. Garcia-Closas M, Kristensen V, Langerod A, Qi Y, Yeager M, Burdett L, Welch R, Lissowska J, Peplonska B, Brinton L, Gerhard DS, Gram IT, Perou CM, Borresen-Dale AL, Chanock S (2007) Common genetic variation in TP53 and its flanking genes, WDR79 and ATP1B2, and susceptibility to breast cancer. Int J Cancer 121:2532–2538
48. Johnson N, Fletcher O, Palles C, Rudd M, Webb E, Sellick G, dos Santos Silva I, McCormack V, Gibson L, Fraser A, Leonard A, Gilham C, Tavtigian SV, Ashworth A, Houlston R, Peto J (2007) Counting potentially functional variants in BRCA1, BRCA2 and ATM predicts breast cancer susceptibility. Hum Mol Genet 16: 1051–1057
49. Franeková M, Zúbor P, Stanclová A, Dussan CA, Bohusová T, Galo S, Dobrota D, Kajo K, Péc M, Racay P (2007) Association of p53 polymorphisms with breast cancer: a case–control study in Slovak population. Neoplasma 54:155–161
50. Pharoah PD, Tyrer J, Dunning AM, Easton DF, Ponder BA, SEARCH Investigators (2007) Association between common variation in 120 candidate genes and breast cancer risk. PloS Genet 3:e42
51. Samson M, Swaminathan R, Rama R, Sridevi V, Nancy KN, Rajkumar T (2007) Role of GSTM1 (Null/Present), GSTP1 (Ile105Val) and P53 (Arg72Pro) genetic polymorphisms and the risk of breast cancer: a case control study from South India. Asian Pac J Cancer Prev 8:253–257
52. Akkiprik M, Sonmez O, Gulluoglu BM, Caglar HB, Kaya H, Demirkalem P, Abacioglu U, Sengoz M, Sav A, Ozer A (2009) Analysis of p53 gene polymorphisms and protein over-expression in patients with breast cancer. Pathol Oncol Res 15:359–368
53. Singh V, Rastogi N, Mathur N, Singh K, Singh MP (2008) Association of polymorphism in MDM-2 and p53 genes with breast cancer risk in Indian women. Ann Epidemiol 18:48–57
54. Lum SS, Chua HW, Li H, Li WF, Rao N, Wei J, Shao Z, Sabapathy K (2008) MDM2 SNP309 G allele increases risk but the Tallele is associated with earlier onset age of sporadic breast cancers in the Chinese population. Carcinogenesis 29:754–761
55. Cavallone L, Arcand SL, Maugard C, Ghadirian P, Mes-Masson AM, Provencher D, Tonin PN (2008) Haplotype analysis of TP53 polymorphisms, Arg72Pro and Ins16, in BRCA1 and BRCA2 mutation carriers of French Canadian descent. BMC Cancer 8:96
56. Costa S, Pinto D, Pereira D, Rodrigues H, Cameselle-Teijeiro J, Medeiros R, Schmitt F (2008) Importance of TP53 codon 72 and intron 3 duplication 16 bp polymorphisms in prediction of susceptibility on breast cancer. BMC Cancer 8:32
57. De Vecchi G, Verderio P, Pizzamiglio S, Manoukian S, Bernard L, Pensotti V, Volorio S, Ravagnani F, Radice P, Peterlongo P (2008) The p53 Arg72Pro and Ins16 bp polymorphisms and their haplotypes are not associated with breast cancer risk in BRCA-mutation negative familial cases. Cancer Detect Prev 32:140–143
58. Nordgard SH, Alnaes GI, Hihn B et al (2008) Pathway based analysis of SNPs with relevance to 5-FU therapy: relation to intratumoral mRNA expression and survival. Int J Cancer 123: 577–585
59. Henrırquez-Hernandez LA, Murias-Rosales A, Herna′ndez GA, Cabrera DLA, Dı′az-Chico BN, Mori DSM, Ferna′ndez PL (2009) Gene polymorphisms in TYMS, MTHFR, p53 and MDR1 as risk factors for breast cancer: a case–control study. Oncol Rep 22: 1425–1433
60. Kazemi M, Salehi Z, Chakosari RJ (2009) TP53 codon 72 polymorphism and breast cancer in northern Iran. Oncol Res 18(1):25–30
61. Denisov EV, Cherdyntseva NV, Litvyakov NV, Slonimskaya EM (2009) TP53 mutations and Arg72Pro polymorphism in breast cancers. Cancer Genet Cytogenet 192:93–95
62. Aoki MN, da Silva AHAC, Amarante MK, do Val Carneiro JL, Fungaro MH, Watanabe MA (2009) CCR5 and p53 codon 72 gene polymorphisms: implications in breast cancer development. Int J Mol Med 23:429–435
63. Song F, Zheng H, Liu B, Wei S, Dai H, Zhang L, Calin GA, Hao X, Wei Q, Zhang W, Chen K (2009) An miR-502-binding site single-nucleotide polymorphism in the 3′-untranslated region of the SET8 gene is associated with early age of breast cancer onset. Clin Cancer Res 15(19):6292–6300
64. Lång A, Palmebäck Wegman P, Wingren S (2009) The significance of MDM2 SNP309 and p53 Arg72Pro in young women with breast cancer. Oncol Rep 22:575–579
65. Hrstka R, Beranek M, Klocova K, Nenutil R, Vojtesek B (2009) Intronic polymorphisms in TP53 indicate lymph node metastasis in breast cancer. Oncol Rep 22:1205–1211
66. Kara N, Karakus N, Ulusoy AN, Ozaslan C, Gungor B, Bagci H (2010) P53 codon 72 and HER2 codon 655 polymorphisms in Turkish breast cancer patients. DNA Cell Biol 29:7
67. Ebner F, Schremmer-Danninger E, Rehbock J (2010) The role of TP53 and p21 gene polymorphisms in breast cancer biology in a well specified and characterized German cohort. J Cancer Res Clin Oncol 136:1369–1375
68. Bisof V, Salihović MP, Narancić NS, Skarić-Jurić T, Jakić-Razumović J, Janićijević B, Turek S, Rudan P (2010) TP53 gene polymorphisms and breast cancer in Croatian women: a pilot study. Eur J Gynaecol Oncol 31(5):539–544
69. Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22:719–748
70. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188
71. Thompson SG, Higgins JPT (2002) How meta-regression analyses be undertaken and ihterpreted? Statist Med 21:1559–1573
72. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50(4): 1088–1101
73. Egger M, Smith DG, Schneider M (1997) Minder C Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629–634
74. Buyru N, Altinisik J, Demokan S, Dalay N (2007) p53 genotypes 153 and haplotypes associated with risk of breast cancer. Cancer Detect Prev 31:207–213