Genet. Res., Camb. (2015), vol. 97, e7. © Cambridge University Press 2015
doi:10.1017/S0016672315000075

Evaluation of the p53 Arg72Pro polymorphism and its association with cancer risk: a HuGE review and meta-analysis

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(*Received 21 June 2014; revised 10 February 2015; accepted 11 March 2015*)

Summary

Codon 72 is a hotspot of polymorphisms in the TP53 gene, which encodes a hub protein in the protein–protein interaction network of p53. It is thus a central player in the apoptotic pathway, preventing cancer. A large number of articles have been published exploring its association with an increased susceptibility to most common cancers. However, these studies have produced inconclusive results, which may be due to their small sample sizes or study designs. To comprehensively evaluate the potential correlation between the TP53 Pro72Arg polymorphism and cancer risk and to better characterize the Pro72Arg polymorphism, we performed a systematic HuGE review and meta-analysis of candidate studies through online resources, according to the proposal of MOOSE and the PRISMA statement. The identified articles were carefully examined according to the inclusion criteria. Pooled odds ratios were calculated on the basis of different genetic models, while heterogeneity was assessed through a chi-based Q-test and I^2. After applying the inclusion filters, we obtained a pool of 54 eligible studies, representing 18 718 cases and 21 261 controls. Overall, non-significant cancer risk was observed in all the genetic models but their observed heterogeneity was extremely significant. In subgroup analysis, an increased susceptibility was observed in the case of colorectal cancer, while in cancers of the female reproductive system, significantly increased risk was detected in all the genetic models except the dominant model. In another subgroup analysis, significantly increased cancer risk was observed among Asians in homozygous and recessive models, while in Americans increased cancer risk was observed only in dominant and recessive models. No association was observed in the rest of the populations. In conclusion, pooled subgroup analysis on the basis of ethnicity proved that the TP53 Arg72Pro polymorphism is associated with an increased risk of cancer in Asians and Americans only and is not associated in other populations. It can therefore be concluded that this meta-analysis of available data suggests partial confirmation of the association between the TP53 Arg72Pro polymorphism and cancer risk susceptibility.

1. Introduction

Cancer, a major threat to humanity, is a multifactorial disorder caused by genetic or environmental factors, or the interactions of these (Bredberg, 2011). Genetic factors include point mutations or chromosomal aberrations, which can result in the breakdown of the relevant pathways and can enhance cancer susceptibility (Zhang *et al.*, 2013).

TP53 is a tumor suppressor gene, encoding a transcription factor (hub protein) in the protein–protein interaction network of p53. It is a central player in the apoptotic pathway that detects internal and external signals and effectors, and induces death in response to a number of cellular stresses, thereby preventing cancer stresses (Vogelstein *et al.*, 2000; Horn & Vousden, 2007). Unfortunately, >50% of human cancers show alterations in this genome guardian (Milner & Medcalf, 1991). More than 20 000 different types of alterations in human TP53 have been observed (Olivier *et al.*, 2002), with the addition of a number of SNPs that have also been proven to differentially enhance cancer susceptibility in different ethnic groups (Packer *et al.*, 2006). They may affect the function of the TP53 gene product through increased enigmatic splicing, altering the stability of the downstream transcript, enhanced mutability or differential expression (Lozano & Levine, 1991; Lozano, 1994).

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Codon 72 is a hotspot of polymorphisms in the TP53 gene. rs1042522 is the most studied SNP at this codon, encoding an Arg–Pro substitution (Sprague *et al.*, 2007). Located in the proline-rich region, it can affect the structure of the SH3-binding domain. The gene product with the Arg residue has been found to be more efficient for apoptotic activity as compared to the counterpart with the Pro residue at codon 72. The allelic/variant frequencies of codon 72 differ among different world populations and also are responsible for differential cancer susceptibility in these populations (Dumont *et al.*, 2003).

In recent years, a large number of studies have been published exploring the association of the TP53 Pro72Arg polymorphism and increased susceptibility to most common cancers, including prostate cancer (PCa). The results of a single study may be underpowered due to certain reasons and it is clear from the literature that these studies have reported conflicting results, which may be due to their small sample sizes or study design (Yang *et al.*, 2012).To comprehensively evaluate the potential correlation between the TP53 Pro72Arg polymorphism and cancer risk, and to further our understanding and to allow for a more precise characterization of the Pro72Arg polymorphism, we designed a systematic HuGE review and meta-analysis of candidate studies.

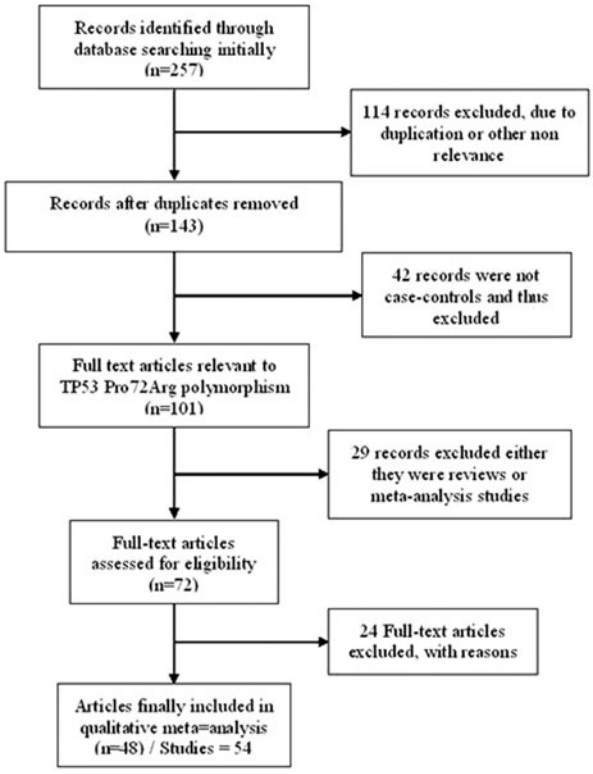

Fig. 1. A general flow diagram of study identification according to MOOSE and PRISMA statement.

2. Materials and methods

This study was undertaken according to the proposal of MOOSE and the PRISMA statement. We performed a systematic search of the relevant literature for articles discussing the TP53 codon 72 (rs1042522) polymorphism and its association with cancer risk. The online resources, including Google scholar, MEDLINE, PubMed and Embase, were used with the combination of terms 'Arg72 or rs1042522, polymorphism or variant or TP53 or SNP' and 'cancer or carcinoma or adenocarcinoma' (From 2000 to 2014). The identified full-length articles were carefully and systematically examined and retrieved by the co-authors. We only included those studies that were in agreement with our inclusion criteria in the meta-analysis, namely: (1) the publication to be included must be a case-control study; (2) the publication must refer to the association of the TP53 codon 72 polymorphism and cancer risk; (3) the publication must refer to both the sample sizes of cases and controls along with distribution of alleles/genotypes or other necessary information that can help to infer results; (4) if multiple publications are available on the same/overlapping data, the publication with the most recent and largest population will be included in the study; and (5) the language of publication was confined to English only.

The data were extracted independently by all the authors from the eligible articles, and then the results were compared. Disagreements, if any, were resolved by discussion and reasoning, and the following information was collected from each study: name of first author, year of publication, study title, total number of samples (cases and controls), type of cancer, ethnicity and distribution of genotypes in case and control groups, as shown in Fig. 1 and Table 1.

We performed the meta-analysis according to the criteria described earlier. Hardy-Weinberg equilibrium (HWE) was calculated using Fisher's exact/chi-square for each study, and $P < 0{\cdot}05$ was considered statistically significant. We only included those studies that were in agreement with HWE. The strength of association between the TP53 Pro72Arg polymorphism and cancer risk was assessed through odds ratios (ORs) along with their 95%CI. Pooled ORs were calculated on the basis of four different genetic models, including CC vs. GG, CC vs. CG, dominant and recessive models. We further subdivided the association by analyzing by ethnicity and cancer type. Ethnicity was classified into Asian, European, American (North and South), Australian and African populations. We assessed heterogeneity through chi-based Q-tests, and $P > 0{\cdot}10$ was considered statistically significant. In cases lacking heterogeneity among the studies, the Mantel-Haenszel (fixed effects) model was

https://doi.org/10.1017/S0016672315000075 Published online by Cambridge University Press

Table 1. *Characteristics of case-control studies included in the meta-analysis.*

S. No	Authors	Population	Disease	Cases				Controls			
				No	GG	GC	CC	No	GG	GC	CC
1.	Boroujeni *et al.* (2013)	Iranian	Breast cancer	135	6	102	27	140	21	93	26
2.	Boroujeni *et al.* (2013)	Iranian	Colorectal cancer	145	18	78	49	140	27	85	28
3.	Medrek *et al.* (2013)	Polish	Ovarian cancer	626	302	265	59	1045	537	436	72
4.	Yoneda *et al.* (2013)	Asian	Endometrial cancer	125	52	55	18	200	75	102	23
5.	Gallegos-Arreola *et al.* (2012)	Mexican	Endometrial cancer	151	66	51	34	235	145	71	19
6.	Proestling *et al.* (2012)	Caucasians	Breast cancer	267	125	123	19	220	125	87	8
7.	Sumbul *et al.* (2012)	Caucasians	Hepatocellular carcinoma	119	21	52	46	119	7	63	49
8.	Dastjerdi (2011)	Iranian	Colorectal cancer	250	52	101	97	250	61	113	76
9.	Di Vuolo *et al.* (2011)	Italian	HCC	61	38	20	3	122	71	42	9
10.	Jha *et al.* (2011)	Indian (Asian)	Gliomas	84	33	27	24	112	15	70	27
11.	Sonoyama *et al.* (2011)	Japanese	Pancreatic cancer	226	33	110	83	448	46	205	197
12.	Yu *et al.* (2011)	Caucasians	SCCHN	1083	593	405	85	1090	597	428	65
13.	Ghasemi *et al.* (2010)	Asian	Endometrial cancer	30	13	15	2	32	7	21	4
14.	Naccarati *et al.* (2010)	Caucasians	Pancreatic cancer	238	88	131	19	743	369	316	58
15.	Ricks-Santi *et al.* (2010)	African	Prostate cancer	245	37	135	73	178	22	86	70
16.	Sameer *et al.* (2010)	Kashmiri (Asian)	Colorectal cancer	86	10	37	39	160	65	63	32
17.	Xu *et al.* (2010)	Asian	Prostate cancer	209	39	129	41	268	42	140	86
18.	Almeida *et al.* (2009)	Brazilian	EABT	90	20	48	22	100	48	42	10
19.	Ashton *et al.* (2009)	Caucasians	Endometrial cancer	191	101	75	15	290	166	107	17
20.	Chang-Claude *et al.* (2009)	Germany	Breast cancer	127	64	49	14	276	160	96	20
21.	Hirata *et al.* (2009)	Asian	Prostate cancer	140	45	75	20	167	61	80	26
22.	Koshiol *et al.* (2009)	Latin American	CIN+	458	206	191	61	376	182	144	50
23.	Mabuchi *et al.* (2009)	Japanese	POAG (NTG)	213	92	95	26	189	83	83	23
24.	Mabuchi *et al.* (2009)	Japanese	POAG (HTG)	212	85	102	25	189	83	83	23
25.	Nunobiki *et al.* (2009)	Asian	Endometrial cancer	102	44	48	10	95	34	54	7
26.	Zubor *et al.* (2009)	Caucasians	Endometrial cancer	121	69	44	8	330	200	113	17
27.	Costa *et al.* (2008)	Portuguese	Sporadic BCa	175	98	61	16	212	124	70	18
28.	Costa *et al.* (2008)	Portuguese	Familial BCa	73	39	25	9	434	256	142	36
29.	Pinto *et al.* (2008)	Southeast Brazil	Gliomas	94	53	34	7	100	48	42	10
30.	Yoon *et al.* (2008)	Korea	HCC	287	66	111	110	296	37	135	124
31.	Schmidt *et al.* (2007)	from HaBCS, Germany	Breast cancer	1043	565	401	77	506	250	217	39
32.	Schmidt *et al.* (2007)	from ABCS Netherlands	Breast cancer	1247	668	477	102	263	141	109	13
33.	Schmidt *et al.* (2007)	from BBC, UK	Breast cancer	517	285	200	32	585	303	237	45
34.	Schmidt *et al.* (2007)	from HeBCS, Finland	Breast cancer	580	294	235	51	365	198	141	26
35.	Schmidt *et al.* (2007)	from SEARCH, UK	Breast cancer	4858	2687	1915	256	5130	2769	1973	388
36.	Samson *et al.* (2007)	Asian	Breast cancer	250	66	125	59	500	135	224	141
37.	Samson *et al.* (2007)	Asian	Breast cancer	250	66	125	59	500	135	224	141
38.	Malmer *et al.* (2007)	Nordic-UK	Gliomas	636	361	241	34	1461	801	556	104
39.	Zhu *et al.* (2007)	Chinese	Colorectal cancer	670	105	321	244	345	85	177	83
40.	Ezzikouri *et al.* (2007)	Caucasians	HCC	96	13	31	52	222	14	79	129
41.	Hirata *et al.* (2007)	Asian	Prostate cancer	167	56	89	22	167	61	80	26
42.	Quinones *et al.* (2006)	Caucasians	Prostate cancer	60	22	24	14	117	59	45	13
43.	Ueda *et al.* (2006)	Asian	Endometrial cancer	108	55	45	8	95	34	54	7
44.	Wu *et al.* (2006)	USA	Bladder cancer	615	390	186	39	598	390	156	52
45.	Leiros *et al.* (2005)	Caucasians	Prostate cancer	39	20	17	2	48	23	23	2
46.	Niwa *et al.* (2005)	Asian	Endometrial cancer	156	53	37	66	442	178	210	54
47.	Agorastos *et al.* (2004)	Caucasians	Endometrial cancer	56	24	28	4	30	6	19	5
48.	Huang *et al.* (2004)	Taiwanese	Prostate cancer	200	66	92	42	247	84	109	54
49.	Leveri *et al.* (2004)	Caucasians	HCC	86	7	33	46	254	19	113	122
50.	Wang *et al.* (2004)	Caucasians	Gliomas	309	165	126	18	342	194	128	20
51.	Wu *et al.* (2004)	Asian	Prostate cancer	92	11	61	20	126	43	53	30

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Table 1. (*Cont.*)

S. No	Authors	Population	Disease	Cases				Controls			
				No	GG	GC	CC	No	GG	GC	CC
52.	Anzola *et al.* (2003)	Caucasians	HCC	97	4	47	46	111	4	42	65
53.	Suzuki *et al.* (2003)	Asian	Prostate cancer	114	48	46	20	105	41	57	7
54.	Henner *et al.* (2001)	Caucasians	Prostate cancer	109	66	41	2	146	93	38	15

ABCS, Amsterdam Breast Cancer Study, Netherlands; BBC, British Breast Cancer, London, UK; CIN, cervical intraepithelial neoplasia; EABT, extra-axial brain tumour; Familial BCa, familial breast cancer; HaBCS, Hannover Breast Cancer Study, Germany; HCC, hepatocellular carcinoma; HeBCS, Helsinki Breast Cancer Study, Finland; SCCHN, squamous cell cancer of the head and neck; SEARCH, Study of Epidemiology & Risk Factors in Cancer Heredity, Cambridge, UK; Sporadic BCa, sporadic breast cancer.

used to calculate the pooled ORs; otherwise, the random effects model was used. I^2 was also calculated to quantitatively assess the percentage of variation among the studies as a result of heterogeneity. The values were classified into four classes to generalize the observed heterogeneity, as follows: zero value = no observed heterogeneity, values > 0 ⩽ 25% = low observed heterogeneity, values > 25% ⩽ 50% = moderate observed heterogeneity, values > 50% ⩽ 75% = high observed heterogeneity and values > 75% = very high observed heterogeneity. We confirmed the stability of the results through the sensitivity analysis, and we examined publication bias through funnel plots and qualitatively by Egger's test. All the statistical analysis was conducted by using comprehensive Meta Analysis Software version 2.2·064.

3. Results

After a comprehensive search, we identified a total of 257 publications and reviewed them using the defined inclusion criteria (Fig. 1). After applying the inclusion filters we obtained a pool of 54 eligible studies, representing a total of 18 718 cases and 21 261controls for the p53 Arg72Pro polymorphism. Some of the included articles consist of more than one study; for these, each study was considered as an independent data set. The main characteristics of all the included data sets are listed in Table 1, and Table 2 consists of the quantitative results of this meta-analysis and their heterogeneity. As shown in Table 2, the data sets included different studies from different world populations, including 24 from Asian, 17 from European, ten from American (North and South), one from Australia and two from African populations.

Overall, non-significantly elevated cancer risk was found in all the genetic models (CC vs. GG, OR: 1·14, 95%CI: 0·96–1·12, I^2 = 77·54, P = 0·000; CC vs. CG, OR: 1·10, 95%CI: 0·96–1·27, I^2 = 70·64, P = 0·000; dominant, OR: 1·07, 95%CI: 0·97–1·17, I^2 = 69·97, P = 0·000; recessive, OR: 1·13, 95%CI: 0·98–1·30, I^2 = 74·85, P = 0·000) but the observed heterogeneity was extremely significant in the models. To further focus our analysis, we stratified the data into subgroups on the basis of cancer types and population/ethnicity. An increased susceptibility was observed in the results of all genetic models in the case of colorectal cancer (CC vs. GG, OR: 2·73, 95%CI: 1·54–4·84, I^2 = 75·19, P = 0·007; CC vs. CG, OR: 1·65, 95%CI: 1·34–2·04, I^2 = 0·00, P = 0·731; dominant, OR: 1·95, 95%CI: 1·20–3·15, I^2 = 73·36, P = 0·010; recessive, OR: 1·93, 95%CI: 1·44–2·59, I^2 = 48·02, P = 0·123), while in cancers of the female reproductive system, significantly increased risk was detected in all the genetic models except the dominant model (CC vs. GG, OR: 1·61, 95%CI: 1·33–1·95, I^2 = 75·09, P = 0·000; CC vs. CG, OR: 1·65, 95%CI: 1·36–2·01, I^2 = 77·99, P = 0·000; recessive: OR: 1·71, 95%CI: 1·42–2·04, I^2 = 79·19, P = 0·000). In the case of pancreatic cancer, only the dominant model (OR: 1·30, 95%CI: 1·01–1·67, I^2 = 90·21, P = 0·001) was found to be associated with increased risk, while no association/significant association was observed for the rest of the cancer types included in the study.

In the subgroup analysis on the basis of ethnicity, significantly increased cancer risk was observed among Asians in CC vs. GG (OR: 1·14, 95%CI: 1·03–1·26, I^2 = 78·73, P = 0·000) and recessive models (CC vs. GG+CG, OR: 1·17, 95%CI: 1·06–1·29, I^2 = 83·07, P = 0·000), while in Americans significantly increased cancer risk was observed in dominant (OR: 1·33, 95%CI: 1·06–1·68, I^2 = 74·82, P = 0·000) and recessive models (OR: 1·22, 95%CI: 1·01–1·46, I^2 = 72·78, P = 0·000). No association was observed in rest of the populations (Table 2).

(i) *Publication bias and sensitivity analysis*

Publication bias was assessed both through the visual inspection of the funnel plots symmetry and the statistical evidence of the Begg's and Mazumdar's rank correlation test and Egger's linear regression method (CC vs. GG, Kendall's tau = 0·015, two tailed

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Table 2. *Pooled analysis of association of P72R (rs1042522) polymorphism and cancer risk.*

	No.	Case/control	CC vs. GG	CC vs. CG	Dominant	Recessive
			OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Total	54	18 718/21 261	1·14 (0·96–1·12) I^2 = 77·15, P = 0·000	1·10 (0·96–1·27) I^2 = 70·64, P = 0·000	1·07 (0·97–1·17) I^2 = 69·97, P = 0·000	1·13 (0·98–1·30) I^2 = 74·85, P = 0·000
Cancer type						
Cancer of the female reproductive system	11	2124/3170	1·61 (1·33–1·95) I^2 = 75·09, P = 0·000	1·65 (1·36–2·01) I^2 = 77·99, P = 0·000	1·02 (0·82–1·26) I^2 = 64·88, P = 0·000	1·71 (1·42–2·04) I^2 = 79·19, P = 0·000
Urologic cancers	11	1990/2167	0·99 (0·69–1·43) I^2 = 62·36, P = 0·003	0·79 (0·57–1·09) I^2 = 60·67, P = 0·005	1·13 (0·93–1·37) I^2 = 42·22, P = 0·068	0·87 (0·64–1·17) I^2 = 60·86, P = 0·004
Breast cancer	12	9522/9131	1·12 (0·87–1·45) I^2 = 67·87, P = 0·000	0·96 (0·79–1·197) I^2 = 48·28, P = 0·031	1·05 (0·94–1·18) I^2 = 51·26, P = 0·020	1·04 (0·84–1·28) I^2 = 59·91, P = 0·004
Brain cancer	5	1213/2115	0·99 (0·48–2·01) I^2 = 79·83, P = 0·001	1·18 (0·73–1·90) I^2 = 57·47, P = 0·052	0·92 (0·55–1·53) I^2 = 87·42, P = 0·000	1·11 (0·70–1·76) I^2 = 59·21, P = 0·044
Head and neck cancers	1	1083/1090	1·32 (0·94–1·85) I^2 = 0·000, P = 1·000	1·38 (0·97–1·96) I^2 = 0·000, P = 1·000	1·0 (0·85–1·19) I^2 = 0·000, P = 1·000	1·34 (0·96–1·88) I^2 = 0·000, P = 1·000
Pancreatic cancer	2	464/1191	0·89 (0·39–2·05) I^2 = 78·79, P = 0·030	0·79 (0·59–1·05) I^2 = 0·000, P = 0·99	1·30 (1·01–1·67) I^2 = 90·21, P = 0·001	0·81 (0·61–1·07) I^2 = 2·20, P = 0·31
Colorectal cancer	4	1151/895	2·73 (1·54–4·84) I^2 = 75·19, P = 0·007	1·65 (1·34–2·04) I^2 = 0·000, P = 0·731	1·95 (1·20–3·15) I^2 = 73·36, P = 0·010	1·93 (1·44–2·59) I^2 = 48·02, P = 0·123
Hepatocellular carcinoma	6	746/1124	0·52 (0·37–0·72) I^2 = 0·000, P = 0. 607	1·02 (0·83–1·26) I^2 = 0·000, P = 0. 534	0·55 (0·41–0·73) I^2 = 17·23, P = 0·302	0·88 (0·72–1·07) I^2 = 0·000, P = 0·628
Optic glaucoma	2	425/378	1·04 (0·66–1·63) I^2 = 0·000, P = 0·931	0·94 (0·60–1·47) I^2 = 0·000, P = 0·810	1·10 (0·83–1·45) I^2 = 0·000, P = 0·66	0·98 (0·64–1·51) I^2 = 0·000, P = 0·93
Ethnicity/populations						
Asian	24	4370/5332	1·17 (0·86–1·59) I^2 = 81·85, P = 0·000	1·14 (1·03–1·26) I^2 = 78·73, P = 0·000	1·01 (0·82–1·26) I^2 = 78·24, P = 0·000	1·17 (1·06–1·29) I^2 = 83·07, P = 0·000
European	17	10 808/12 087	1·07 (0·86–1·35) I^2 = 62·24, P = 0·000	1·00 (0·83–1·20) I^2 = 48·32, P = 0·014	1·05 (0·95–1·17) I^2 = 52·93, P = 0·005	1·03 (0·85–1·26) I^2 = 58·68, P = 0·001
American (North and South)	10	3008/3152	1·36 (0·87–2·013) I^2 = 77·03, P = 0·000	1·10 (0·76–1·60) I^2 = 64·31, P = 0·003	1·33 (1·06–1·68) I^2 = 74·82, P = 0·000	1·22 (1·01–1·46) I^2 = 72·78, P = 0·000
Australian	1	191/290	1·45 (0·69–3·03) I^2 = 0·000, P = 1·000	1·26 (0·59–2·68) I^2 = 0·000, P = 1·000	1·19 (0·83–1·72) I^2 = 0·000, P = 1·000	1·37 (0·67–2·81) I^2 = 0·000, P = 1·000
African	2	341/400	0·55 (0·33–0·89) I^2 = 0·000, P = 0·497	0·80 (0·53–1·23) I^2 = 37·40, P = 0·206	0·62 (0·35–1·12) I^2 = 33·63, P = 0·220	0·73 (0·54–1·0) I^2 = 0·000, P = 0·413

CI, confidence intervals, I^2, percentage of variation across studies as a result of heterogeneity; OR, odds ratio.

P = 0·86; Egger: bias = 0·93 [95% CI: -0·28–2·14], two tailed P = 0·05; CC vs. CG, Kendall's tau = 0·1, two tailed P = 0·3; Egger: bias = 1·11 [95%CI: -0·02–2·24], two tailed P = 0·053; dominant, Kendall's tau = -−0·07, two tailed P = 0·42; Egger: bias = 0·36 [95% CI: -0·52–1·26], two tailed P = 0·41; recessive, Kendall's tau = 0·1, two tailed P = 0·30; Egger: bias = 1·08 [95%CI: -0·14–2·31], two tailed P = 0·08).

4. Discussion

We explored the association of the TP53 P72R polymorphism and increased cancer susceptibility in this study, including 54 eligible case-control studies representing 18 718 cases and 21 261 controls. We observed that the presence of the TP53 P72R polymorphism showed no association with increased cancer susceptibility in the overall pooled analysis, while in the subgroup analysis, the cancer risk was significantly pronounced in colorectal cancer and cancers of the female reproductive system. However, no significant association of the polymorphism was observed in the rest of the cases.

TP53 is one of the most widely explored genes because of its role as a tumor suppressor, playing a major role both in cancer development and progression. There were many epidemiological studies available on its genetic association, expounding the correlation of the TP53 P72R polymorphism and increased cancer risk, but their results were controversial (Anzola *et al.*, 2003; Yoon *et al.*, 2008; Di Vuolo *et al.*, 2011; Sumbul *et al.*, 2012). The conflicting results may partially be due to the small sample sizes of the studies and sampling effects, because each of these studies typically involved relatively few cases and controls.

(i) *Hepatocellular carcinoma*

Chen *et al.* (2011) studied the correlation of the TP53 R72P polymorphism and hepatocellular carcinoma (HCC) risk, including six studies. They were unable to provide any evidence of an association in Caucasians and Asians. Similar results were published in another study by Xu *et al.* (2012) based on ten case-control studies with a total of 2026 cases and 2733 controls. In subgroup analyses stratified on the basis of ethnicity, they showed that the polymorphism was associated with increased risk of HCC in Caucasians under the allelic contrast model (C vs. G, OR: 1·20, 95%CI: 1·03–1·41), homozygous model (CC vs. GG, OR: 1·74, 95%CI: 1·23–2·47) and recessive model (CC vs. CG+GG, OR: 1·85, 95%CI: 1·33–2·57). They further reported that the TP53 Arg72Pro polymorphism may have a race-specific effect on HCC risk. Lv *et al.* (2013) performed another meta-analysis on the same topic, including 11 case-control studies with a total of 2718 cases and 3752 controls. Overall, significantly increased risk of HCC was identified among carriers of the homozygous genotype CC vs. GG (OR: 1·38, 95%CI: 1·03–1·85) and recessive model (CC vs. CG+GG, OR: 1·28, 95%CI: 1·03–1·59). In the subgroup analysis, on the basis of ethnicity, increased risk of HCC was observed in their results in Asians and Caucasians. In Asians, association was observed in the recessive model (CC vs. GG+CG, OR: 1·17, 95%CI: 1·02–1·34), while in Caucasians association was observed in the homozygous model (CC vs. GG, OR: 1·65, 95%CI: 1·07–2·56) and recessive model (CC vs. CG+GG, OR: 1·74, 95%CI: 1·14–2·66). This meta-analysis suggests that the TP53 Arg72Pro polymorphism may play a critical role in HCC development, and gender and family history may not modulate the effect of this polymorphism on HCC risk. Hu *et al.* (2014) also examined the validity of the TP53 Arg72Pro polymorphism and its association with increased susceptibility of HCC. They identified 15 eligible studies with 3704 cases and 4559 controls, but their results did not support any association in between the Pro (C) allele and HCC risk. However, subgroup analysis showed significant associations between the G to C polymorphism and susceptibility to HCC when stratifying by race etc. In Asians, G vs. C, OR: 0·39, 95%CI: 0·36–0·41; GG vs. CC, OR: 0·85, 95%CI: 0·74–0·98; CG vs. CC, OR: 0·88, 95%CI: 0·78–1·00; GG+CG vs. CC, OR: 0·87, 95%CI: 0·78–0·98; in the Caucasian population, C vs. G, OR: 0·27, 95%CI: 0·24–0·32; GG vs. CC, OR: 0·61, 95%CI: 0·39–0·94; CG vs. CC, OR: 0·55, 95%CI; 0·35–0·87; GG+CG vs. CC, OR: 0·57, 95%CI; 0·38–0·88. This meta-analysis suggests that the TP53 Arg72Pro polymorphism may be associated with increased risk of HCC, especially in subgroup analysis of Asian and Caucasian populations.

(ii) *Sarcoma*

Chang and Yu (2014) designed a study to examine the association between the p53 codon 72 polymorphism and sarcoma risk among Caucasians. Their results did not provide any statistical evidence for significant sarcoma risk associated with the TP53 codon 72 polymorphism (G vs. C, OR: 1·03, 95%CI: 0·90–1·18; GG vs. CC, OR: 1·00, 95%CI: 0·80–1·26; GG+CG vs. CC, OR: 0·99, 95%CI; 0·83–1·19; GG vs. CG+CC, OR: 1·09, 95%CI: 0·89–1·35; CG vs. CC, OR: 0·95, 95% CI: 0·71–1·27). They also did not find any significant links in the subgroup analysis on the basis of ethnicity and sarcoma type. Their results therefore suggest that the TP53 codon 72 polymorphism may not play a role in sarcoma development in the Caucasian population.

https://doi.org/10.1017/S0016672315000075 Published online by Cambridge University Press

(iii) *Glioma*

He *et al*. (2013) performed a meta-analysis on the association between the TP53 codon 72 polymorphism and glioma risk, but no pronounced association was observed in their overall pooled analysis (C vs. G, OR: 1·04, 95%CI: 0·90–1·20; CC vs. GG, OR: 0·95, 95%CI: 0·80–1·14; CG vs. GG, OR: 1·01, 95%CI: 0·79–1·29; CG+CC vs. GG, OR: 1·03, 95%CI: 0·82–1·29; CC vs. GG+CG, OR: 1·02, 95%CI: 0·86–1·22). In subgroup analysis, the polymorphism was again proven to have no affect on glioma risk in population-based, hospital-based, astrocytoma and oligodendroglioma studies among Caucasians. Similar results were also produced by other researchers (Zhu *et al.*, 2014) in their study, performed on similar disorders (the allele contrast, OR: 1·04, 95%CI: 0·94–1·16; CC vs. GG, OR: 1·01, 95%CI: 0·83–1·22; the dominant model, OR: 1·02, 95%CI; 0·93–1·12; recessive model, OR: 1·06, 95%CI: 0·88–1·28; and the heterozygote genotypes: CG vs. GG, OR: 1·03, 95%CI: 0·90–1·17, P = 0·082). In the subgroup analysis stratified by ethnicity, neither the subjects of Asian descent nor the subjects of Caucasian descent showed any effect on glioma risk. Another meta-analysis of the same disorder and same polymorphism also showed that there is no association between the TP53 Arg72Pro polymorphism and increased risk of glioma (C vs. G, OR: 1·02, 95%CI: 0·85–1·22; CC vs. GG, OR: 1·06, 95%CI: 0·85–1·34; CC+CG vs. GG, OR: 1·07, 95%CI: 0·91–1·27), and the same results were again observed in the subgroup analysis by ethnicity especially in Caucasians. However, a slight association was recorded in the case of Asians (OR: 1·42, 95% CI: 1·00–2·02) (Zhang *et al.*, 2014). It can therefore be inferred that there is limited available evidence for an association between the TP53 codon 72 polymorphism and glioma risk and thus more comprehensive and systematic studies are needed to provide a more comprehensive evaluation of this polymorphism in Asians.

(iv) *Urologic cancers*

Li *et al*. (2010) investigated bladder cancer in their meta-analysis performed with six studies, and found that the patients had a comparatively lower frequency of CG genotypes (OR: 0·80, 95%CI: 0·64–0·99). In the subgroup analysis, Caucasian patients were found to have a higher frequency of GG (OR: 1·64, 95%CI: 1·18–2·28) than CG (OR: 0·62, 95%CI: 0·44–0·86). In another subgroup analysis on the basis of cancer stage, they further observed that the invasive bladder cancers had comparatively lower frequency of GG (OR: 0·58, 95%CI: 0·36–0·93) and higher frequency of CG (OR: 0·62, 95%CI: 0·44–0·86) than the non-invasive bladder cancers. On the basis of these results they suggested that the TP53 Arg72Pro polymorphism is significantly associated with bladder cancer and its genotypic distribution varies with the cancer stage. Another group of researchers determined more precisely the relationship between the p53 Arg72Pro polymorphism and PCa risk. Their analysis was based on 17 case-control studies involving 2371 PCa cases and 2854 controls. In the overall pooled analysis, their results showed a non-significant association between the TP53 Arg72Pro polymorphism and PCa risk in all genetic models. However, significant association was observed in Caucasians in the co-dominant (OR: 1·57, 95%CI: 1·08–2·28, P = 0·017) and recessive model (CC vs. CG+GG, OR: 1·60, 95%CI: 1·12–2·27, P = 0·009) when the included studies were limited only to those conforming the Hardy-Weinberg equilibrium (Lu *et al.*, 2014). It was therefore concluded that the CC genotype of the TP53 Arg72Pro polymorphism is significantly associated with increased risk of PCa in Caucasians.

(v) *Cancers of the female reproductive system*

Tang *et al*. (2012) performed a meta-analysis to estimate any possible correlation between the TP53 Arg72Pro polymorphism and endometrial cancer. Nine published studies, with a total of 829 cases and 1387 controls, were included in the study. Their overall pooled results suggested a non-significant association between the TP53 Arg72Pro polymorphism and cancer risk, especially in Caucasians and Asians in any of the genetic models (additive model, OR: 1·027, 95%CI: 0·893–1·18, P = 0·71; recessive model, OR: 1·099, 95%CI: 0·802–1·507, P = 0·556; dominant model, OR: 1·013, 95%CI: 0·842–1·219, P = 0·89). A recent study performed by Alqumber *et al*. (2014) investigated the association between the TP53 Arg72Pro polymorphism and susceptibility to ovarian cancer. The meta-analysis, which was based on 12 studies including 993 cases and 1264 controls, showed non-significant association (C vs. G, OR: 0·980, 95% CI: 0·677–1·419; CC vs. GG, OR: 0·731, 95%CI: 0·341–1·564; CG vs. GG, OR: 1·237, 95%CI: 0·862–1·773; dominant model, OR: 1·089, 95%CI: 0·706–1·681; recessive model, OR: 0·754, 95%CI: 0·428–1·329). Similar results were recorded in the subgroup analysis stratified by ethnicity in the Caucasian population.

There are many studies available investigating the association of the TP53 Arg72Pro polymorphism and the risk of other cancers. Dai *et al.* (2009) suggested in their meta-analysis performed on 32 case-control studies that the Pro allele of the TP53 Arg72Pro polymorphism was emerging as a low-penetrance susceptibility allele for the development of lung cancer. Zhou *et al*. (2007) observed that the TP53 Arg72Pro polymorphism was significantly

https://doi.org/10.1017/S0016672315000075 Published online by Cambridge University Press

associated with gastric cancer among Asians. They also suggested that variations in genotype distribution may be due to location, stage and histological differentiation. Similar results were produced in another study conducted on cervical cancer. The researchers found that the TP53 GG genotype at codon 72 did not seem to represent a risk marker for the development of cervical lesions in the majority of the European countries studied (Sousa *et al.*, 2007).

We tried our best to include the most recent publications in our study. Our results are consistent with those of Zhang *et al.* (2011), who also observed non-significant association between the TP53 Pro72Arg polymorphism and overall PCa risk (allelic contrast, RR: 1·02, 95%CI: 0·96–1·09; homozygous model, RR: 1·12, 95%CI: 0·74–1·70; heterozygous model, RR: 1·22, 95%CI: 0·94–1·60; dominant model, RR: 1·05, 95%CI: 1·00–1·11; recessive model, RR: 0·96, 95% CI: 0·67–1·37). They also found the same results in a stratified analysis in all genotype models by ethnicity. Moreover, no associations of the TP53 Arg72Pro polymorphism with colorectal cancer (Dahabreh *et al.*, 2010) and breast cancer (Ma *et al.*, 2010) risk were observed.

The limitations of our meta-analysis include the following: (1) Some of the included studies have rather small sample sizes, which were technically not satisfactory to determine any possible association in between the TP53 Arg72Pro polymorphism and cancer risk; (2) cancer being a multi-factorial, complex disease, different interactions such as gene–gene, gene–environment and protein–protein interactions may be further evaluated to better understand the complexities in depth; and (3) the majority of the literature is focused on the association between the TP53 Arg72pro polymorphism and cancer risk, which are usually not concerned with the haplotype effects on cancer development.

In the present meta-analysis, there were 24 studies from Asians, 17 from Europe, ten from America (North and South), two from Africa and one from Australia. Pooled subgroup analysis on the basis of ethnicity showed that the TP53Arg72Pro polymorphism is associated with increased risk of cancer only in Asians and Americans but not in other populations. On the basis of our results, it can be inferred that this association is still vague in different populations, and so more studies with larger sample sizes are needed for more systematic and comprehensive assessment, especially in Asians. It can therefore be concluded that, this meta-analysis of available data suggests partial confirmation of the association between the TP53 Arg72Pro polymorphism and cancer risk susceptibility.

The authors would like to extend thanks to Ms Raisa Bano and Mr Shahid Hussain for their technical assistance.

Author contributions

All the authors were directly involved in the whole process, therefore it is disclosed that all the authors contributed equally towards the research.

Declaration of interest

None.

References

Agorastos, T., Masouridou, S., Lambropoulos, A. F., Chrisafi, S., Miliaras, D., Pantazis, K., Constantinides, T. C., Kotsis, A. & Bontis, I. (2004). P53 codon 72 polymorphism and correlation with ovarian and endometrial cancer in Greek women. *European Journal of Cancer Prevention* **13**, 277–280.

Almeida, L. O., Custodio, A. C., Pinto, G. R., Santos, M. J., Almeida, J. R., Clara, C. A., Rey, J. A. & Casartelli, C. (2009). Polymorphisms and DNA methylation of gene TP53 associated with extra-axial brain tumors. *Genetics and Molecular Research* **8**, 8–18.

Alqumber, M. A., Akhter, N., Haque, S., Panda, A. K. & Mandal, R. K. (2014). Evaluating the association between p53 codon 72 Arg>Pro polymorphism and risk of ovary cancer: a meta-analysis. *PLoS ONE* **9**, e94874.

Anzola, M., Cuevas, N., Lopez-Martinez, M., Saiz, A., Burgos, J. J. & de Pancorbo, M. M. (2003). Frequent loss of p53 codon 72 Pro variant in hepatitis C virus-positive carriers with hepatocellular carcinoma. *Cancer Letters* **193**, 199–205.

Ashton, K. A., Proietto, A., Otton, G., Symonds, I., McEvoy, M., Attia, J., Gilbert, M., Hamann, U. & Scott, R. J. (2009). Polymorphisms in TP53 and MDM2 combined are associated with high grade endometrial cancer. *Gynecologic Oncology* **113**, 109–114.

Boroujeni, H. R., Karimi, M., Moshkelani, S. & Parsaei, P. (2013). Association of the p53 codon 72 polymorphism with breast cancer in central part of Iran. *African Journal of Pharmacy and Pharmacology* **7**, 356–359.

Bredberg, A. (2011). Cancer: more of polygenic disease and less of multiple mutations? A quantitative viewpoint. *Cancer* **117**, 440–445.

Chang-Claude, J., Ambrosone, C. B., Lilla, C., Kropp, S., Helmbold, I., von Fournier, D., Haase, W., Sautter-Bihl, M. L., Wenz, F., Schmezer, P. & Popanda, O. (2009). Genetic polymorphisms in DNA repair and damage response genes and late normal tissue complications of radiotherapy for breast cancer. *British Journal of Cancer* **100**, 1680–1686.

Chang, Z. & Yu, X. (2014). Association between p53 codon 72 polymorphism and sarcoma risk among Caucasians. *Tumour Biology* **35**, 4807–4812.

Chen, X., Liu, F., Li, B., Wei, Y. G., Yan, L. N. & Wen, T. F. (2011). p53 codon 72 polymorphism and liver cancer susceptibility: a meta-analysis of epidemiologic studies. *World Journal of Gastroenterology* **17**, 1211–1218.

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.

Dahabreh, I. J., Linardou, H., Bouzika, P., Varvarigou, V. & Murray, S. (2010). TP53 Arg72Pro polymorphism

and colorectal cancer risk: a systematic review and meta-analysis. *Cancer Epidemiology, Biomarkers & Prevention* **19**, 1840–1847.

Dai, L., Gast, A., Horska, A., Schrappe, M., Bartram, C. R., Hemminki, K., Kumar, R. & Bermejo, J. L. (2009). A case-control study of childhood acute lymphoblastic leukaemia and polymorphisms in the TGF-(beta) and receptor genes. *Pediatric Blood & Cancer* **52**, 819–823.

Dastjerdi, M. N. (2011). TP53 codon 72 polymorphism and P53 protein expression in colorectal cancer specimens in Isfahan. *Acta Medica Iranica* **49**, 71–77.

Di Vuolo, V., Buonaguro, L., Izzo, F., Losito, S., Botti, G., Buonaguro, F. M. & Tornesello, M. L. (2011). TP53 and MDM2 gene polymorphisms and risk of hepatocellular carcinoma among Italian patients. *Infectious Agents and Cancer* **6**, 13.

Dumont, P., Leu, J. I., Della Pietra, A. C. 3rd, George, D. L. & Murphy, M. (2003). The codon 72 polymorphic variants of p53 have markedly different apoptotic potential. *Nature Genetics* **33**, 357–365.

Ezzikouri, S. E., Feydi, A. E. & Chafik, A. (2007). The Pro variant of the p53 codon 72 polymorphism is associated with hepatocellular carcinoma in Moroccan population. *Hepatology Research* **37**, 748–754.

Gallegos-Arreola, M. P., Figuera-Villanueva, L. E., Puebla-Perez, A. M., Montoya-Fuentes, H., Suarez-Rincon, A. E. & Zuniga-Gonzalez, G. M. (2012). Association of TP53 gene codon 72 polymorphism with endometriosis in Mexican women. *Genetics and Molecular Research* **11** (2), 1401–1408.

Ghasemi, N., Karimi-Zarchi, M., Mortazavi-Zadeh, M. R. & Atash-Afza, A. (2010). Evaluation of the frequency of TP53 gene codon 72 polymorphisms in Iranian patients with endometrial cancer. *Cancer Genetics and Cytogenetics* **196**, 167–170.

He, F., Xia, Y., Liu, H., Li, J. & Wang, C. (2013). P53 codon 72 GG polymorphism and glioma risk: an updated meta-analysis. *Tumour Biology* **34**, 3121–3130.

Henner, W. D., Evans, A. J., Hough, K. M., Harris, E. L., Lowe, B. A. & Beer, T. M. (2001). Association of codon 72 polymorphism of p53 with lower prostate cancer risk. *Prostate* **49**, 263–266.

Hirata, H., Hinoda, Y., Kikuno, N., Kawamoto, K., Dahiya, A. V., Suehiro, Y., Tanaka, Y. & Dahiya, R. (2007). CXCL12 G801A polymorphism is a risk factor for sporadic prostate cancer susceptibility. *Clinical Cancer Research* **13**, 5056–5062.

Hirata, H., Hinoda, Y., Kikuno, N., Suehiro, Y., Shahryari, V., Ahmad, A. E., Tabatabai, Z. L., Igawa, M. & Dahiya, R. (2009). Bcl2 -938C/A polymorphism carries increased risk of biochemical recurrence after radical prostatectomy. *Journal of Urology* **181**, 1907–1912.

Horn, H. F. & Vousden, K. H. (2007). Coping with stress: multiple ways to activate p53. *Oncogene* **26**, 1306–1316.

Hu, S., Zhao, L., Yang, J. & Hu, M. (2014). The association between polymorphism of P53 Codon72 CG and hepatocellular carcinoma susceptibility: evidence from a meta-analysis of 15 studies with 3,704 cases. *Tumour Biology* **35**, 3647–3656.

Huang, S. P., Wu, W. J., Chang, W. S., Wu, M., T., Chen, Y. Y., Chen, Y. J., Yu, C. C., Wu, T. T., Lee, Y. H., Huang, J. K. & Huang, C. H. (2004). p53 codon 72 and p21 codon 31 polymorphisms in prostate cancer. *Cancer Epidemiology, Biomarkers & Prevention* **13**, 2217–2224.

Jha, P., Jha, P., Pathak, P., Chosdol, K., Suri, V., Sharma, M. C., Kumar, G., Singh, M., Mahapatra, A. K. & Sarkar, C. (2011). TP53 polymorphisms in gliomas from Indian patients: study of codon 72 genotype, rs1642785, rs1800370 and 16 base pair insertion in intron-3. *Experimental Molecular Pathology* **90**, 167–172.

Koshiol, J., Hildesheimm, A., Gonzalez, P., Bratti, M. C., Porras, C., Schiffman, M., Herrero, R., Rodriguez, A. C., Wacholder, S., Yeager, M., Chanock, S. J., Burk, R. D. & Wang, S. S. (2009). Common genetic variation in TP53 and risk of human papillomavirus persistence and progression to CIN3/cancer revisited. *Cancer Epidemiology, Biomarkers & Prevention* **18**, 631–637.

Leiros, G, J., Galliano, S. R., Sember, M. E, Kahn, T., Schwarz, E. & Eiguchi, K. (2005). Detection of human papillomavirus DNA and p53 codon 72 polymorphism in prostate carcinomas of patients from Argentina. *BMC Urology* **5**, 15.

Leveri, M., Gritti, C. & Rossi, L. (2004). Codon 72 polymorphism of P53 gene does not affect the risk of cirrhosis and hepatocarcinoma in HCV-infected patients. *Cancer Letters* **208**, 75–79.

Li, D. B., Wei, X., Jiang, L. H., Wang, Y. & Xu, F. (2010). Meta-analysis of epidemiological studies of association of P53 codon 72 polymorphism with bladder cancer. *Genetics and Molecular Research* **9**, 1599–1605.

Lozano, G. & Levine, A. J. (1991). Tissue-specific expression of p53 in transgenic mice is regulated by intron sequences. *Molecular Carcinogenesis* **4**, 3–9.

Lozano, J. S. (1994). Introns: evolution and function. *Current Opinion in Genetics & Development* **4**, 823–831.

Lu, Y., Liu, Y., Zeng, J., He, Y., Peng, Q., Deng, Y., Wang, J., Xie, L., Li, T., Qin, X. & Li, S. (2014). Association of p53 codon 72 polymorphism with prostate cancer: an update meta-analysis. *Tumour Biology* **35**, 3997–4005.

Lv, L., Wang, P., Zhou, X. & Sun, B. (2013). Association between the p53 codon 72 CG polymorphism and hepatocellular carcinoma risk. *Tumour Biology* **34**, 1451–1459.

Ma, Y., Yang, J., Liu, Z., Zhang, P., Yang, Z., Wang, Y. & Qin, H. (2010). 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 Research and Treatment* **125**, 201–205.

Mabuchi, F., Sakurada, Y., Kashiwagi, K., Yamagata, Z., Iijima, H. & Tsukahara, S. (2009). Lack of association between p53 gene polymorphisms and primary open angle glaucoma in the Japanese population. *Molecular Vision* **15**, 1045–1049.

Malmer, B. S., Feychting, M., Lonn, S., Lindstrom, S., Gronberg, H., Ahlbom, A., Schwartzbaum, J., Auvinen, A., Collatz-Christensen, H., Johansen, C., Kiuru, A., Mudie, N., Salminen, T., Schoemaker, M. J., Swerdlow, A. J. & Henriksson, R. (2007). Genetic variation in p53 and ATM haplotypes and risk of glioma and meningioma. *Journal of Neuro-Oncology* **82**, 229–237.

Mędrek, K., Magnowski, P., Masojc, B., Chudecka-Głaz, A., Torbe, B., Menkiszak, J., Spaczyński, M., Gronwald, J., Lubinski, J. & Gorski, B. (2013). Association of common WRAP 53 variant with ovarian cancer risk in the Polish population. *Molecular Biology Reports* **40**, 2145–2147.

Milner, J. & Medcalf, E. A. (1991). Cotranslation of activated mutant p53 with wild type drives the wild-type p53 protein into the mutant conformation. *Cell* **65**, 765–774.

Naccarati, A., Pardini, B., Polakova, V., Smerhovsky, Z., Vodickova, L., Soucek, P., Vrana, D., Holcatova, I., Ryska, M. & Vodicka, P. (2010). Genotype and haplotype analysis of TP53 gene and the risk of pancreatic cancer: an association study in the Czech Republic. *Carcinogenesis* **31**, 666–670.

Niwa, Y., Hirose, K., Matsuo, K., Tajima, K., Ikoma, Y., Nakanishi, T., Nawa, A., Kuzuya, K., Tamakoshi, A. & Hamajima, N. (2005). Association of p73 G4C14-to-A4T14 polymorphism at exon 2 and p53 Arg72Pro polymorphism with the risk of endometrial cancer in Japanese subjects. *Cancer Letters* **219**, 183–190.

Nunobiki, O., Ueda, M., Yamamoto, M., Toji, E., Sato, N., Izuma, S., Okamoto, Y., Torii, K. & Noda, S. (2009). Polymorphisms of p53 codon 72 and MDM2 promoter 309 and the risk of endometrial cancer. *Human Cell* **22**, 101–106.

Olivier, M., Eeles, R., Hollstein, M., Khan, M. A., Harris, C. C. & Hainaut, P. (2002). The IARC TP53 database: new online mutation analysis and recommendations to users. *Human Mutation* **19**, 607–614.

Packer, B. R., Yeager, M., Burdett, L., Welch, R., Beerman, M., Qi, L., Sicotte, H., Staats, B., Acharya, M., Crenshaw, A., Eckert, A., Puri, V., Gerhard, D. S. & Chanock, S. J. (2006). SNP500Cancer: a public resource for sequence validation, assay development, and frequency analysis for genetic variation in candidate genes. *Nucleic Acids Research* **34**, D617–D621.

Pinto, G. R., Yoshioka, F. K., Silva, R. L., Clara, C. A., Santos, M. J., Almeida, J. R., Burbano, R. R., Rey, J. A. & Casartelli, C. (2008). Prognostic value of TP53 Pro47Ser and Arg72Pro single nucleotide polymorphisms and the susceptibility to gliomas in individuals from Southeast Brazil. *Genetics and Molecular Research* **7**, 207–216.

Proestling, K., Hebar, A., Pruckner, N., Marton, E., Vinatzer, U. & Schreiber, M. (2012). The Pro allele of the p53 codon 72 polymorphism is associated with decreased intratumoral expression of BAX and p21, and increased breast cancer risk. *PLoS One* **7**, e47325.

Quinones, L. A., Irarrazabal, C. E., Rojas, C. R., Orellana, C. E., Acevedo, C., Huidobro, C., Varela, N. E. & Caceres, D. D. (2006). Joint effect among p53, CYP1A1, GSTM1 polymorphism combinations and smoking on prostate cancer risk: an exploratory genotype-environment interaction study. *Asian Journal of Andrology* **8**, 349–355.

Ricks-Santi, L., Mason, T., Apprey, V., Ahaghotu, C., McLauchlin, A., Josey, D., Bonney, G. & Dunston, G. M. (2010). p53 Pro72Arg polymorphism and prostate cancer in men of African descent. *Prostate* **70**, 1739–1745.

Sameer, A. S., Shah, Z. A., Syeed, N., Banday, M. Z., Bashir, S. M., Bhat, B. A. & Siddiqi, M. A. (2010). TP53 Pro47Ser and Arg72Pro polymorphisms and colorectal cancer predisposition in an ethnic Kashmiri population. *Genetics and Molecular Research* **9**, 651–660.

Samson, M., Swaminathan, R., Rama, R., Sridevi, V., Nancy, K. N. & 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 Pacific Journal of Cancer Prevention* **8**, 253–257.

Schmidt, M. K., Reincke, S., Broeks, A., Braaf, L. M., Hogervorst, F. B., Tollenaar, R. A., Johnson, N., Fletcher, O., Peto, J., Tommiska, J., Blomqvist, C., Nevanlinna, H. A., Healey, C. S., Dunning, A. M., Pharoah, P. D., Easton, D. F., Dork, T., Van't Veer, L. J. & Breast Cancer Association Consortium (2007). Do MDM2 SNP309 and TP53 R72P interact in breast cancer susceptibility? A large pooled series from the breast cancer association consortium. *Cancer Research* **67**, 9584–9590.

Sonoyama, T., Sakai, A., Mita, Y., Yasuda, Y., Kawamoto, H., Yagi, T., Yoshioka, M., Mimura, T., Nakachi, K., Ouchida, M., Yamamoto, K. & Shimizu, K. (2011). TP53 codon 72 polymorphism is associated with pancreatic cancer risk in males, smokers and drinkers. *Molecular Medicine Reports* **4**, 489–495.

Sousa, H., Santos, A. M., Pinto, D. & Medeiros, R. (2007). Is the p53 codon 72 polymorphism a key biomarker for cervical cancer development? A meta-analysis review within European populations. *International Journal of Molecular Medicine* **20**, 731–741.

Sprague, B. L., Trentham-Dietz, A., Garcia-Closas, M., Newcomb, P. A., Titus-Ernstoff, L., Hampton, J. M., Chanock, S. J., Haines, J. L. & Egan, K. M. (2007). Genetic variation in TP53 and risk of breast cancer in a population-based case control study. *Carcinogenesis* **28**, 1680–1686.

Sumbul, A. T., Akkız, H., Bayram, S., Bekar, A., Akgollu, E. & Sandıkci, M. (2012). p53 codon 72 polymorphism is associated with susceptibility to hepatocellular carcinoma in the Turkish population: a case-control study. *Molecular Biology Reports* **39**, 1639–1647.

Suzuki, K., Matsui, H., Ohtake, N., Nakata, S., Takei, T., Nakazato, H., Okugi, H., Koike, H., Ono, Y., Ito, K., Kurokawa, K. & Yamanaka, H. (2003). A p53 codon 72 polymorphism associated with prostate cancer development and progression in Japanese. *Journal of Biomedical Science* **10**, 430–435.

Tang, W., He, X., Chan, Y. & Luo, Y. (2012). Lack of association between p53 codon 72 polymorphism and endometrial cancer: a meta-analysis. *Cancer Epidemiology* **36**, e153–e157.

Ueda, M., Terai, Y., Kanda, K., Kanemura, M., Takehara, M., Yamaguchi, H., Nishiyama, K., Yasuda, M. & Ueki, M. (2006). Germline polymorphism of p53 codon 72 in gynecological cancer. *Gynecologic. Oncology* **100**, 173–178.

Vogelstein, B., Lane, D. & Levine, A. J. (2000). Surfing the p53 network. *Nature* **408**, 307–310.

Wang, L. E., Bondy, M. L., Shen, H., El-Zein, R., Aldape, K., Cao, Y., Pudavalli, V., Levin, V. A., Yung, W. K. & Wei, Q. (2004). Polymorphisms of DNA repair genes and risk of glioma. *Cancer Research* **64**, 5560–5563.

Wu, H. C., Chang, C. H., Chen, H. Y., Tsai, F. J., Tsai, J. J. & Chen, W. C. (2004). p53 gene codon 72 polymorphism but not tumor necrosis factor-alpha gene is associated with prostate cancer. *Urology International* **73**, 41–46.

Wu, X., Gu, J., Grossman, H. B., Amos, C. I., Etzel, C., Huang, M., Zhang, Q., Millikan, R. E., Lerner, S., Dinney, C. P. & Spitz, M. R. (2006). Bladder cancer predisposition: a multigenic approach to DNA-repair and cell-cycle-control genes. *American Journal of Human Genetics* **78**, 464–479.

Xu, B., Xu, Z., Cheng, G., Min, Z. C., Mi, Y., Zhang, Z. Z., Tao, J., Li, P. C., Wang, M. L., Tang, J. L., Zhang, Z. D., Zhang, W., Wu, H. F., Feng, N. H. & Hua, L. X. (2010). Association between polymorphisms of TP53 and MDM2 and prostate cancer risk in southern Chinese. *Cancer Genetics and Cytogenetics* **202**, 76–81.

Xu, C. T., Zheng, F., Dai, X., Du, J. D., Liu, H. R., Zhao, L. & Li, W. M. (2012). Association between TP53 Arg72Pro polymorphism and hepatocellular carcinoma risk: a meta-analysis. *Asian Pacific Journal of Cancer Prevention* **13**, 4305–4309.

Yang, J., Xu, D. L., Lu., Q., Han, Z. J., Tao, J., Lu, P., Wang, C., Di, X. K. & Gu, M. (2012). Prostate cancer risk and aggressiveness associated with the CYP1B1 4326C/G (Leu432Val) polymorphism: a meta-analysis of 2788 cases and 2968 controls. *Asian Journal of Andrology* **14**, 560–565.

Yoneda, T., Kuboyama, A., Kato, K., Ohgami, T., Okamoto, K., Saito, T. & Wake, N. (2013). Association

of MDM2 SNP309 and TP53 Arg72Pro polymorphisms with risk ofendometrial cancer. *Oncology Reports* **30**, 25–34.

Yoon, Y. J., Chang, H. Y., Ahn, S. H., Kim, J. K., Park, Y. K., Kang, D. R., Park, J. Y., Myoung, S. M., Kim do, Y., Chon, C. Y. & Han, K. H. (2008). MDM2 and p53 polymorphisms are associated with the development of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. *Carcinogenesis* **29**, 1192–1196.

Yu, H., Huang, Y. J., Liu, Z., Wang, L. E., Li, G., Sturgis, E. M., Johnson, D. G. & Wei, Q. (2011). Effects of MDM2 promoter polymorphisms and p53 codon 72 polymorphism on risk and age at onset of squamous cell carcinoma of the head and neck. *Molecular Carcinogenesis* **50**, 697–706.

Zhang, F., Li, D., Li, Y., Li, H., Sun, J., Li, X. & Li, X. (2014). Quantitative assessment of the association between TP53Arg72Pro polymorphism and risk of glioma. *Tumour Biology* **35**, 747–751.

Zhang, H., Li, L. & Xu, Y. (2013). CYP1B1 polymorphisms and susceptibility to prostate cancer: a meta-analysis. *PLoS ONE* **8**, e68634.

Zhang, L., Shao, N., Yu, Q., Hua, L., Mi, Y. & Feng, N. (2011). Association between p53 Pro72Arg polymorphism and prostate cancer risk: a meta-analysis. *Journal of Biomedical Research* **25**, 25–32.

Zhou, Y., Li, N., Zhuang, W., Liu, G. J., Wu, T. X., Yao, X., Du, L., Wei, M. L. & Wu, X. T. (2007). P53 codon 72 polymorphism and gastric cancer: a meta-analysis of the literature. *International Journal of Cancer* **121**, 1481–1486.

Zhu, W., Lu, L., Li, Y., Yao, J. & Xu, B. (2014). The effects of p53 Arg72Pro polymorphism on glioma susceptibility: a meta-analysis. *Tumour Biology* **35**, 3725–3730.

Zhu, Z. Z., Wang, A. Z., Jia, H. R., Jin, X. X., He, X. L., Hou, L. F. & Zhu, G. (2007). Association of the TP53 codon 72 polymorphism with colorectal cancer in a Chinese population. *Japanese Journal of Clinical Oncology* **37**, 385–90.

Zubor, P., Stanclova, A., Kajo, K., Hatok, J., Klobusiakova, D., Visnovsky, J. & Danko, J. (2009). The p53 codon 72 exon 4 BstUI polymorphism and endometrial cancer in Caucasian women. *Oncology* **76**, 173–183.