

TP53 Arg72Pro Polymorphism and Colorectal Cancer Risk: A Systematic Review and Meta-Analysis

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Abstract

Background: The *TP53* rs1042522 polymorphism (c.215C>G, Arg72Pro) has been extensively investigated as a potential risk factor for colorectal cancer, but the results have thus far been inconclusive.

Methods: We searched multiple electronic databases to identify studies investigating the association between the Arg72Pro polymorphism and colorectal cancer. Individual study odds ratios (OR) and their confidence intervals were estimated using allele-frequency, recessive, and dominant genetic models. Summary ORs were estimated using random effects models.

Results: We identified 23 eligible case-control studies, investigating 6,514 cases and 9,334 controls. There was significant between-study heterogeneity for all genetic models. The control group in one of the studies was not in Hardy-Weinberg equilibrium; only three studies reported that genotyping was blinded to case/control status and five studies used tumor tissue for case genotyping. Overall, we did not identify any association between rs1042522 and colorectal cancer risk under an allele-frequency comparison (OR, 0.99; 95% confidence interval, 0.89–1.09). Likewise, no association was evident under dominant or recessive models. Studies using tumor tissue for case genotyping found a protective effect for the Pro allele, compared with studies using somatic DNA ($P_{\text{interaction}} = 0.03$). Results were also inconsistent between different genotyping methods ($P_{\text{interaction}} = 0.03$).

Conclusion: We did not identify an association between *TP53* rs1042522 and colorectal cancer. Published results seem to be driven by technical artifacts rather than true biological effects.

Impact: Future genetic association studies should use more rigorous genotyping methods and avoid the use of tumor tissue as a source of DNA to prevent genotype misclassification due to loss of heterozygosity. *Cancer Epidemiol Biomarkers Prev*; 19(7); 1840–7. ©2010 AACR.

Introduction

Colorectal cancer is the third most common type of cancer in the United States and is responsible for approximately 50,000 deaths per year (1). Family-based studies have suggested that the disease has a significant genetic component, with a large twin study conducted in Scandinavian countries suggesting that as many as 35% of colorectal cancers may be due to inherited susceptibility (2). However, the recognized Mendelian predisposition syndromes, such as hereditary nonpolyposis colorectal cancer and adenomatous polyposis coli, account for less than

5% of the overall incidence of colorectal cancer (3). Therefore, common, low-penetrance polymorphisms may confer a substantial part of the genetic risk, but given that the estimated effect of each polymorphism is expected to be small, large studies are necessary to reduce the size-related uncertainty of effects and provide robust evidence of association.

The *TP53* gene, located at 17p13, is a prototypical tumor suppressor gene encoding a 53-kDa protein (p53) with important functions in cell cycle control, apoptosis, and maintenance of DNA integrity (4–6). The importance of p53 in cell cycle regulation (via gene transcription) and DNA integrity is such that it has been called the “guardian of the genome” (7). The function of p53 is to reduce the incidence of cancers by mediating apoptosis in cells that have activated oncogenic pathways. Similarly, DNA damage or genotoxic stress may cause the induction of p53, leading to growth arrest or apoptosis (8). Germ-line mutations in *TP53* are known to cause a number of recognized human cancers including Li-Fraumeni syndrome (9). When *TP53* itself is not genetically inactivated, other mechanisms, such as loss of heterozygosity by deletion of the 17p locus or gene methylation, may contribute to reduced p53 activity (10–15). The polymorphic nature of the *TP53* gene and its central role in

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cell cycle regulation have highlighted it as a good potential candidate susceptibility gene for colorectal cancer. Although several *TP53* polymorphisms have been investigated as risk factors for cancer, by far the most extensively investigated is a nonsynonymous polymorphism in a proline-rich domain located in exon 4, where a cytosine (C; variant allele) for guanine (G) substitution results in the substitution of proline (Pro) for arginine (Arg) at codon 72 of the p53 protein (Arg72Pro, refSNP no. rs1042522; ref. 16). Various lines of evidence indicate that these two alleles differ in their capacities to induce target gene transcription, their interaction with p73, their targeting of the proteasome, and their susceptibility to degradation by human papillomavirus E6 protein (17-20). They are also recognized as modulating apoptosis at differing rates (21).

Several epidemiologic studies have addressed the influence of this polymorphism on cancer risk for most common cancer types, including colorectal cancer; however, small sample sizes and deficiencies in study design have contributed to conflicting results (22-26). To offer a comprehensive evaluation of the potential association of this polymorphism with colorectal cancer risk, we conducted a systematic review and meta-analysis of candidate genetic association studies.

Materials and Methods

Study eligibility and data extraction

We sought to identify genetic association studies published before July 31, 2009, investigating the association between the rs1042522 polymorphism located within the *TP53* gene and colorectal cancer, using computer-based searches (last search: July 31, 2009) of MEDLINE (PubMed), the Human Genome Epidemiology Network (HuGE Net) Literature Finder, and the NIH Genetic Association Database (27), using keywords related to the *TP53* gene and colorectal cancer (the full search strategy is available from the authors on request). Additionally, we searched two *TP53*-specific databases that collect information related to *TP53* polymorphisms: the IARC *TP53* database (28) and the p53 website (29). We also hand-searched the reference lists for all retrieved studies and relevant review articles, as well as journals known to publish studies relevant to the topic.

Studies using an analytic design (case-control, nested case-control, or cohort) and employing validated genotyping methods to examine the frequency of rs1042522 among colorectal cancer patients and controls were eligible for inclusion. Family-based studies were not considered eligible owing to different design considerations. Studies that included patients known to have hereditary colorectal cancer syndromes, such as nonpolyposis colorectal cancer or familial adenomatous polyposis, were excluded. If studies reported on mixed populations of syndromic and sporadic colorectal cancer, we only used the genotype information for patients with sporadic disease (when available). We only considered studies published in English.

The following information was abstracted from each study: first author, journal, year of publication, study design, matching, ethnicity of participants, definition and numbers of cases and controls, DNA extraction and genotyping methods, source of genetic material for genotyping cases, frequency of genotypes, anatomic location of the tumor (colon versus rectum), and the number of cases and controls for each *TP53* genotype. Data extraction was done independently by two reviewers (I.J.D. and V.V.) and discrepancies were resolved by consensus including a third reviewer (S.M.).

Evidence synthesis

For our main analysis, we compared allele frequencies (the proline-encoding allele C versus the arginine-encoding allele G) between cases and controls. We also evaluated a recessive (CC versus CG+GG) and a dominant model (CC+CG versus GG) for the C allele. All associations were presented as odds ratios (OR) with their corresponding 95% confidence interval (95% CI). Between-study heterogeneity was tested using the χ^2 -based *Q*-statistic and was considered statistically significant at $P < 0.1$ (30). Between-study inconsistency was quantified using the I^2 statistic (31). A pooled OR was estimated based on the individual study ORs using random-effects (DerSimonian and Laird) models (32). Cumulative meta-analysis was carried out to evaluate the trend of the random-effects OR over time (33).

Cancer subtype (colon versus rectum), participant ethnicity (individuals of White ancestry versus East Asian), Hardy-Weinberg equilibrium (HWE) in the control group, matching of cases and controls, genotyping quality control (repeat genotyping of a random selection of samples), blinded genotyping (genotyping by individuals blinded to the case/control status of each individual versus lack of blinding or no mention of blinding), and source of DNA for cases (use of tumor tissue obtained during surgery versus blood/normal tissue) were prespecified as characteristics for assessment of heterogeneity by subgroup analysis. When a study explicitly stated that pathologic examination was used to select healthy tissue obtained by surgery, we considered the study along with studies that used blood samples, given the high sensitivity and specificity of pathologic diagnosis for discriminating healthy and cancer tissues. We also performed sensitivity analysis by excluding such studies.

Assessment of bias

The differential magnitude of effect in large versus small studies was assessed using the Harbord modification of the Egger test (34, 35). A test for interaction was used to compare the results of the first study with the pooled estimate of all subsequent studies and to compare pooled effect estimates between studies (36). The distribution of the genotypes in the control group was tested for HWE using an exact test (37). Studies with controls not in HWE were subjected to a sensitivity analysis in which the effect of excluding specific studies was

Table 1. Characteristics of eligible studies

Author, year	No. cases/controls	Selection of controls	Pro allele frequency in cases/controls (%)	Genotyping method	Source of DNA for cases	Control group in HWE
Olschwang, 1991	71/115	Independent individuals from the CEPH	31/35	PCR-RFLP	Blood	Yes
Kawajiri, 1993	84/347	Unrelated individuals randomly selected from a pool of 2,500 healthy individuals from a prospective cohort	38/35	AS-PCR	Blood	Yes
Sjalander, 1995	155/206	Placental samples from deliveries at the Umea University hospital; UC controls were excluded	33/29	PCR-RFLP	Blood	Yes
Murata, 1996	115/152	Patients with noncancerous pulmonary disease from the outpatient of the same hospital where cases were sampled	36/40	AS-PCR	Blood	Yes
Wang, 1999	61/140	Healthy individuals ages ≥ 65 y	43/44	PCR-RFLP	Cancer tissue	Yes
Sayhan, 2001	67/76	Healthy volunteers with no evidence of cancer or gastrointestinal disease	39/44	PCR-RFLP	Cancer tissue	Yes
Hamajima, 2002	147/241	Noncancer patients who underwent gastroscopy at the same hospital from which the cases were sampled	36/40	PCR-CTPP	Blood	Yes
Gemignani, 2004	352/316	Patients admitted to departments of the same hospital from which cases were sampled	24/21	primer extension	Blood	Yes
Schneider-Stock, 2004	76/85	Healthy individuals	30/31	Melting curve	Blood	Yes
Kruger, 2005	126/245	Healthy blood donors	21/23	PCR-RFLP	Blood	Yes
Sotamaa, 2005	186/323	99 adult individuals representing a weighted sample of the Finish population and 224 male blood donors from the same geographic region as the patients	23/27	PCR-SSCP	Blood	Yes
Koushik, 2006	442/904	For women: cancer-free participants from the NHS; for men: cancer-free participants from the PHS	27/26	TaqMan	Blood	Yes
Perez, 2006	53/109	Healthy individuals	23/35	AS-PCR	Cancer tissue	Yes
Perfumo, 2006	60/188	Patients with a negative colonoscopy, hospital controls, and blood donors	28/20	PCR-RFLP	Blood	Yes
Webb, 2006	2,558/2,694	Healthy individuals recruited among spouses or unrelated friends of the patients with malignancies	25/26	Illumina Bead Arrays	Blood	Yes
Tan, 2007	467/563	Randomly selected from population registers	19/22	Sequencing	Blood	Yes
Zhu, 2007	345/670	Cancer-free individuals randomly selected from a cancer screening program	50/40	PCR-RFLP	Blood	Yes
Csejtej, 2008	102/97	Healthy individuals from archived data	20/21	AS-PCR	Cancer tissue	Yes
Dakouras, 2008	93/95	Healthy individuals	33/45	AS-PCR	Cancer tissue	No
Grünhage, 2008	96/220	Individuals in whom colonoscopy did not reveal abnormal mucosal growth. Those with personal/family history of cancer were excluded.	25/26	PCR-RFLP	Blood	Yes

(Continued on the following page)

Table 1. Characteristics of eligible studies (Cont'd)

Author, year	No. cases/controls	Selection of controls	Pro allele frequency in cases/controls (%)	Genotyping method	Source of DNA for cases	Control group in HWE
Mammano, 2008	90/643	Two control groups were used: 321 healthy individuals and 322 centenarians	31/35	PCR-RFLP	Blood	Yes [per study report]
Cao, 2009	156/293	Healthy individuals	44/37	PCR-RFLP	Normal mucosal cells	Yes
Polakova, 2009	612/612	Individuals undergoing colonoscopic investigation	28/27	PCR-RFLP	Blood	Yes

NOTE: Percentages have been rounded to the nearest integer. Further details are provided in Supplementary Table S1. Abbreviations: AS, allele-specific; CEPH, Centre d'Etude du Polymorphisme Humain (Human Polymorphism Study Center); CTPP, confronting two-pair primers; HWE, Hardy-Weinberg equilibrium; NHS, Nurses Health Study; PHS, Physicians' Health Study; QC, quality control. HWE was tested in the control groups using an exact test (34). SSCP, single-strand conformation polymorphism; UC, ulcerative colitis.

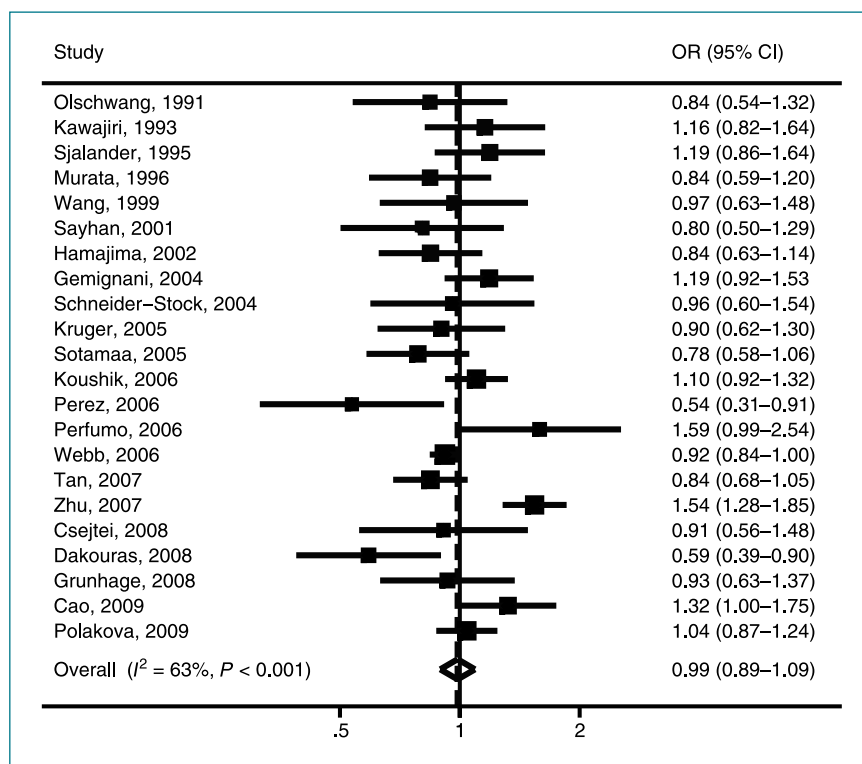
examined. Analyses were performed using Stata (version 11/SE, Stata Corp.) and statistical significance was defined as a two-sided P value <0.05 for all tests except those for heterogeneity.

Results

Our initial search identified 5,035 studies, of which 62 were considered potentially eligible for inclusion in this review and were retrieved in full text. Of those, 37 were

excluded (9 did not include colorectal cancer patients, 8 did not include control groups, 8 did not assess the polymorphism of interest, 5 were not published in English, 4 included patients with hereditary colorectal cancer syndromes, 2 were preclinical studies, and 1 was an editorial) and 25 were considered eligible for the meta-analysis (references to excluded studies are available on request). Of those, one study did not provide extractable data (38) and one used an unconventional genotyping method (DNA pooling; ref. 39) and was included only

Figure 1. Forest plot for the allele-frequency comparison (C versus G) using random effects calculations. Each study is shown by the point estimate of the OR (square proportional to the weight of each study) and 95% CI (extending lines). Studies are listed by year of publication.



in sensitivity analyses. For the main analysis, 23 studies were considered eligible, of which one provided data only for the recessive model (40); the first was published in 1991 and the last in 2009 (40-62). Detailed study characteristics are presented in Table 1 and Supplementary Table S1. In total, 23 studies investigated 6,514 colorectal cancer cases and 9,334 controls for the Arg72Pro polymorphism (mean number of cases, 283; median, 115; min, 53; max, 2,558). Sixteen studies had healthy individuals as controls, and seven studies matched cases and controls (all for age, and five of those for gender). Nine studies used some form of genotyping quality control and only three reported that genotyping was blinded to the case-control status of participants. In one study, the distribution of the genotypes in the control group was not in HWE (Fisher's exact test, $P < 0.05$). Five studies used tumor tissue obtained during surgery for determining the case genotype.

The overall analysis investigating the association between C allele and risk of colorectal cancer relative to the G allele (C versus G) revealed significant between-study heterogeneity ($P_Q < 0.001$; $I^2 = 63\%$) and the random-effects OR was nonsignificant (OR, 0.99; 95% CI, 0.89–1.09; $P = 0.80$; Fig. 1). Moreover, the recessive model for the C allele (CC versus CG+GG) showed moderate heterogeneity ($P = 0.02$, $I^2 = 44\%$) and no evidence of an association (OR, 1.01; 95% CI, 0.84–1.21; Supplementary Fig. S1A). Similarly, the dominant model for the C allele (CC+CG versus GG) showed significant heterogeneity ($P < 0.001$, $I^2 = 65\%$) and the random-effects OR was nonsignificant (OR, 1.00; 95% CI, 0.88–1.15; Supplementary Fig. S1B).

In cumulative meta-analysis of allele-frequency contrasts, the pooled OR has remained centered on 1 over time, indicating that rs1042522 is an unlikely risk variant for colorectal cancer (Supplementary Fig. S2).

Potential for bias

There was no evidence of a differential magnitude of effects in large versus small studies (Harbord/Egger test $P > 0.5$ for all genetic contrasts). In addition, there was no significant difference between the OR of the first study versus the pooled random-effects OR of all subsequent studies under any genetic model, and between-study heterogeneity remained significant after excluding the first study from all analyses ($P_Q < 0.001$ for the allele-frequency and dominant models, and $P_Q = 0.02$ for the recessive genetic model).

Subgroup and sensitivity analyses

Overall, we did not find evidence of effect heterogeneity between studies that reported the use of quality control for genotyping or those where genotyping was performed blinded to the case/control status of participants, compared with those that did not. Although few studies stratified cases into colon and rectal cancer subgroups, the effect of rs1042522 was null in both. Studies using RFLP genotyping methods suggested that the Pro

allele was associated with an increased risk of colorectal cancer (OR, 1.12; 95% CI, 0.96–1.30), compared with studies using alternative genotyping methods (OR, 0.91; 95% CI, 0.82–1.01). The difference was statistically significant ($P_{\text{interaction}} = 0.03$). Furthermore, the ORs from studies using tumor tissue for case genotyping showed a protective effect for the Pro allele (OR, 0.75; 95% CI, 0.60–0.94). In contrast, studies using blood/normal tissue did not detect an association (OR, 1.04; 95% CI, 0.94–1.15); this difference was statistically significant ($P_{\text{interaction}} = 0.03$). In addition, studies of East Asian populations seemed to produce more exaggerated effect sizes compared with studies in Caucasian populations ($P_{\text{interaction}} = 0.03$). Finally, inclusion of the study that used DNA pooling also did not affect the results under any genetic model (data not shown; ref. 39). Table 2 summarizes the results of subgroup analysis for the allele-frequency comparison. Supplementary Table S2 summarizes the results of subgroup analyses using different genetic models.

Discussion

Colorectal cancer is estimated to have a significant heritable component, which is not completely accounted for by the high-penetrance mutations responsible for the known Mendelian colorectal cancer predisposition syndromes (3). The *TP53* rs1042522 polymorphism, one of the most widely investigated polymorphisms in genetic epidemiology, has been considered a good candidate genetic risk factor for many cancers (23). This meta-analysis, based on 6,514 cases and 9,334 controls, shows that this polymorphism is an unlikely risk factor for colorectal cancer. Our results are supportive of the findings of the largest study of this polymorphism in colorectal cancer conducted to date by a collaborative effort of British investigators (61), which did not identify an association between rs1042522 and colorectal cancer. Most importantly, several potential factors that may lead to bias seem to be active in this field. For example, only three studies specifically mentioned that genotyping was blinded to case/control status, and only nine studies implemented some form of genotyping quality control.

Subgroup analysis showed that the ORs from studies of East Asian individuals were exaggerated compared with those investigating Caucasian individuals ($P_{\text{interaction}} = 0.03$). Most likely, this is a spurious finding and does not represent a true biological difference (63, 64). Furthermore, use of RFLP methods for genotyping produced significantly different results compared with other genotyping methods ($P_{\text{interaction}} = 0.03$). This discrepancy between genotyping methods highlights the need for implementing rigorous quality control procedures in future studies, but it is unclear whether the interaction of genotyping method and genetic effect is due to bias in calling uncertain results, or if use of RFLP methods is a surrogate for study quality in general (48). In addition, subgroup

Table 2. Subgroup and sensitivity analyses

Subgroups	No. studies (cases, controls)	Heterogeneity P_Q (I^2)	OR (95% CI); P value	$P_{interaction}$
All studies	22 (6,424, 8,691)	<0.001 (63)	1.00 (0.90–1.10); 0.93	NA
Cancer type				
Colon cancer	4 (574, 1,829)	0.13 (47)	1.21 (0.97–1.50); 0.10	NA
Rectal cancer	4 (293, 1,829)	0.09 (54)	1.13 (0.83–1.53); 0.44	
Ethnicity of participants				
Whites	13 (4,961, 5,647)	0.27 (17)	0.93 (0.86–1.01); 0.08	0.03
East Asians	7 (968, 2,031)	0.004 (68)	1.15 (0.93–1.43); 0.19	
HWE in the control group				
Controls in HWE	21 (6,331, 8,596)	<0.001 (61)	1.01 (0.91–1.11); 0.89	0.07
Controls violating HWE	1 (93, 95)	NA	0.59 (0.39–0.90); 0.01	
Genotyping material*				
Blood, normal tissue	17 (6,048, 8,174)	<0.001 (64)	1.04 (0.94–1.15); 0.48	0.03
Tumor tissue	5 (376, 517)	0.31 (17)	0.75 (0.60–0.94); 0.01	
Genotyping quality control				
Performed	9 (4,621, 5,950)	0.15 (34)	0.99 (0.90–1.09); 0.86	0.79
Not performed or not reported	13 (1,803, 2,741)	<0.001 (72)	0.95 (0.79–1.15); 0.63	
Blind genotyping				
Performed	3 (165, 176)	0.03 (71)	1.06 (0.84–1.34); 0.63	0.53
Not performed or not reported	19 (5,359, 6,931)	<0.001 (64)	0.97 (0.86–1.09); 0.61	
Matching				
Matched design	7 (2,413, 3,257)	<0.001 (79)	1.03 (0.85–1.25); 0.77	0.43
No matching	15 (4,011, 5,434)	0.09 (35)	0.96 (0.86–1.06); 0.39	
Genotyping method				
Other genotyping methods	12 (4,675, 5,926)	0.05 (44)	0.91 (0.82–1.01); 0.08	0.03
RFLP	10 (1,749, 2,765)	0.01 (57)	1.12 (0.96–1.30); 0.17	

NOTE: Significant results are highlighted in bold.

Abbreviation: NA, not applicable.

*One study (38) explicitly stated that “normal mucosal cells were obtained from the cancer-free colorectal mucosa” and was included with the “blood/normal tissue.” Exclusion of this study did not substantially alter our results [blood/normal tissue group: OR, 1.03 (95% CI, 0.93–1.15) $P_{interaction} = 0.04$]. All calculations are based on random effects models and allele-frequency comparisons. Supplementary Table S2 extends these analyses to dominant and recessive genetic models.

analysis revealed that the ORs from studies using cancer tissue for genotyping the cases were significantly ($P = 0.03$) different from the pooled point estimate of studies using blood/normal tissue. In general, use of tumor-derived DNA for determining the constitutional genotype is discouraged because multiple deletional somatic events that occur in tumor cells early in the carcinogenic process may skew the overall results. Loss of heterozygosity often occurs in colorectal cancer, in many cases involving large genomic regions. There is also evidence that allelic loss at the *TP53* locus is nonrandom, and that tumor cells preferentially retain the Arg allele, in different cancer types (19, 57, 65, 66). Regarding colorectal cancer in particular, studies in heterozygous individuals have shown that there is a preferential retention of the Arg allele that may cause genotype misclassification (57). This misclassification would tend to bias the results of genetic association studies toward a detrimental effect of the Arg allele (i.e., a spurious protective effect for the Pro allele). Interestingly, similar re-

sults were reached in a recent pooled analysis of individual patient data from 49 studies in cervical cancer (24). Overall, laboratory artifacts, rather than true biological effects, seem to drive the observed associations of Arg72Pro with colorectal cancer.

It should be noted that the pooled effect estimate based on studies using appropriate DNA sources is in itself not accurate enough to exclude the possibility of a small effect of the rs1042522 polymorphism on colorectal cancer risk, indicating that further research may be necessary to provide conclusive evidence for this variant. Another important limitation of the existing literature is the lack of information about potential gene-gene or gene-environment interactions. Given that the role of several environmental factors in the pathogenesis of colorectal cancer is established, further research should be performed in this direction.

In conclusion, this systematic review and meta-analysis of genetic association studies shows that *TP53* Arg72Pro

is unlikely to be a major risk factor for colorectal cancer. Several sources of bias, including the use of inappropriate genotyping material and the lack of quality control, need to be addressed in the design of future studies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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