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Original Article

The associations between MDM4 rs4245739 A>C polymorphism and cancer risk: a meta-analysis

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Abstract: Recent studies have reported that the single nucleotide polymorphism (SNP) rs4245739 in MDM4 is associated with cancer risk. However, published studies have shown inconsistent results. Therefore, an up to date meta-analysis was performed to investigate the association between rs4245739 and cancer risk in the literature. 10 relevant studies involving 19,915 cases and 61,135 controls were included in this meta-analysis. We observed that rs4245739 was significantly associated with a decreased cancer risk in genetic models (AC vs. AA: OR = 0.85, 95% CI = 0.75-0.96; AC+CC vs. AA: OR = 0.84, 95% CI = 0.74-0.95); C vs. A: OR = 0.86, 95% CI = 0.78-0.96). Moreover, in the subgroup analysis by ethnicity, MDM4 rs4245739 polymorphism was significantly associated with cancer isk in the Asian population. Additionally, an increased ESCC (Esophageal Squamous Cell Carcinoma) risk was found in the recessive and homozygous genetic models after stratification of cancer types. In conclusion, these meta-analysis results suggest that MDM4 rs4245739 polymorphism was associated with a significantly decreased risk of cancer, especially in Asian populations. However, a trend of increased risk of cancer was observed in ESCC.

Keywords: MDM4, rs4245739, cancer risk, polymorphism

Introduction

Cancer is a disease that causes death worldwide, as such it has become a global health problem [1]. It is expected to rank as the most important obstacle to increasing life expectancy and is the main cause of death in every country of the world in the 21st century. According to the latest GLOBOCAN estimates, there will be an estimated 18.1 million new cancer cases and 9.6 million cancer deaths in 2018 [2]. A combination of factors may contribute to cancer, including tobacco use, being overweight, diet, infection, culture, environmental and/or genetic factors [3]. Moreover, previous research has clarified that genetic factors play a significant role in cancer susceptibility [4].

MDM4, also known as MDMX or HDMX, is a structural homologue of mouse double-minute protein 2 (MDM2) and shares a NH2 terminal P53-binding domain with MDM2 [5-9]. P53 is a tumor-suppressor protein, and it plays an important role in many physiological processes, including metabolism and maintenance of genomic stability [10]. Moreover, its inactivation promotes the development of cancer [11]. The main players of the p53 pathway are MDM2 and its homolog MDM4 [12]. Overexpression of MDM4 in human malignancies in combination with MDM2 may inhibit P53 activity, which may contribute to induce spontaneous tumorigenesis and accelerate tumorigenesis [13]. Furthermore, MDM4 has been reported to be upregulated in a variety of human cancers, including retinoblastoma (65%) pre-adult B-cell leukemia (80%), stage II-V melanoma (65%), head and neck squamous cell carcinoma (39%), colon cancer (19%) and breast cancer (19%) [14-18]. Based on the above studies, it can be inferred that genetic variations in the MDM4 gene may be closely related to cancer risk.

Table 1. Characteristics of eligible studies

Author	Year	Cancer type	Ethnicity	Case				Control				HEW
				AA	AC	CC	ALL	AA	AC	CC	ALL	
Closas [24]	2013	Breast	Caucasian	3318	2637	557	6512	22825	15798	2828	41451	0.183
Gao [31]	2015	Lung	Asian	297	22	1	320	548	90	2	640	0.399
Gao [31]	2015	Lung	Asian	183	17	0	200	321	77	2	400	0.248
Pedram N [30]	2016	Breast	Asian	123	87	10	220	165	81	14	260	0.335
Zhou [27]	2013	ESCC	Asian	501	37	2	540	478	70	2	550	0.740
Zhou [27]	2013	ESCC	Asian	529	56	3	588	510	88	2	600	0.379
Liu [29]	2013	Breast	Asian	733	67	0	800	686	111	3	800	0.505
Liu [29]	2013	Breast	Asian	278	22	0	300	501	96	3	600	0.483
Hashemi [28]	2018	Breast	Asian	175	83	7	265	142	76	9	221	0.919
Ziba [26]	2017	Thyroid	Asian	63	34	5	102	144	76	12	232	0.635
Fan [25]	2014	NHL	Asian	187	13	0	200	346	53	1	400	0.487
Gansmo [13]	2015	Prostate	Caucasian	1412	927	161	2500	1021	736	120	1877	0.410
Gansmo [13]	2015	Lung	Caucasian	715	515	101	1331	2042	1439	266	3747	0.566
Gansmo [13]	2015	Breast	Caucasian	966	643	108	1717	1021	703	146	1870	0.106
Gansmo [13]	2015	Colon	Caucasian	823	600	108	1531	2042	1439	266	3747	0.566
Gansmo [23]	2016	Endometrial	Caucasian	757	541	106	1404	1021	703	146	2050	0.106
Gansmo [23]	2016	Ovarian	Caucasian	716	564	105	1367	1021	703	146	2050	0.106

HWE, Hardy-Weinberg equilibrium, ESCC, esophageal squamous cell carcinoma; NHL, non-Hodgkin lymphoma.

Previous studies have shown that the single nucleotide polymorphism (SNP) rs4245739 A>C creates a miR-191 target site that affects the stability of MDM4 mRNA, thereby affecting the expression of MDM4, which is associated with cancer risk [19].

To confirm the association between MDM4 rs4245739 A>C polymorphism and cancer risk, we conducted this up to date meta-analysis by pooling all eligible studies to calculate the estimation of overall cancer risk and evaluated the influence of cancer types and ethnicity.

Materials and methods

Literature search

System searchs through PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), retrieved all relevant literature (prior to October, 2018). The following search subject words were used: "MDM4", "SNP rs4245739 or SNP34091" and "cancer or carcinoma or tumor or neoplasm". We also searched for references to relevant literature to avoid omissions.

Inclusion and exclusion criteria

All of the eligible articles had to meet the following inclusion criteria: (1) studies that evaluated the associations between SNP rs4245739 in MDM4 with cancer risk, (2) studies on human beings, (3) case-control study, (4) all cancers are clinically and pathologically diagnosed (5) the gene frequency data provided are detailed and sufficient to calculate odds ratios (ORs) and 95% confidence intervals (CIs) and *P* values. Exclusion criteria were: (1) duplicated data; (2) case reports, letters, review articles.

Data extraction

The following information was extracted carefully from all eligible studies: first author's name, publication year, cancer type (Breast cancer, Lung cancer, Esophageal cancer, Thyroid carcinoma, NHL, Prostatic cancer, Colon cancer, Endometrial cancer, Ovarian cancer), ethnicity (Caucasian, Asian), numbers of AA, AC, CC genotypes in cases and controls, and *P* value for Hardy-Weinberg equilibrium (HWE) in controls (**Table 1**).

Statistical analysis

First, the Pearson χ^2 test was used to assess whether the genotype frequency of the rs4245739 polymorphism in the control was consistent with the Hardy-Weinberg equilibrium (HWE). Then, statistical analysis of all data was done using Stata 11.0 software. Crude OR and

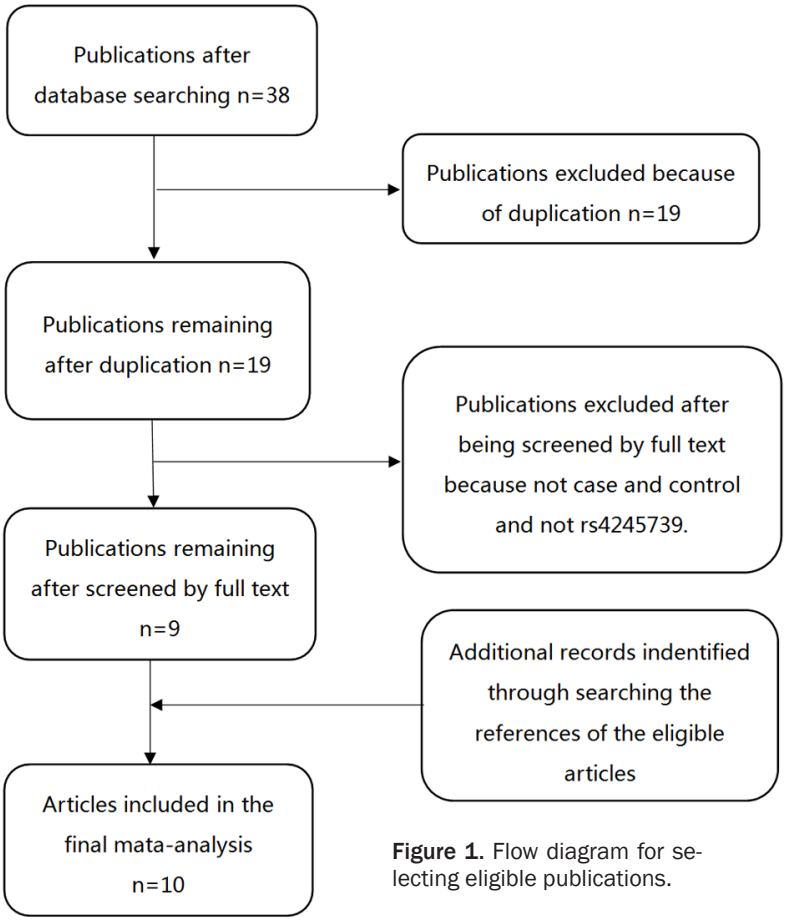


Figure 1. Flow diagram for selecting eligible publications.

95% CI were used to assess the strength of the association between the five models of MDM4 rs4245739 A>C polymorphism and overall cancer risk, the following five models were homozygous (CC vs. AA), heterozygous (AC vs. AA), recessive (CC vs. AC+AA), dominant (AC+CC vs. AA), and allele (C vs. A). Subgroup analysis was carried out by ethnicity and cancer type. $P<0.05$ is considered statistically significant. χ^2-based Q test was used to assess heterogeneity, and $P<0.10$ was considered significant. The I^2 value (0%-100%) is used to determine heterogeneity. When heterogeneity is greater than 50% ($I^2>50\%$), a random-effects models (combined heterogeneity) was used [20]. Otherwise, the fixed-effects model (Ignore heterogeneity) was used [21]. We also performed a sensitivity analyses by excluding each study in turn to evaluate the heterogeneity and its impact on stability of overall results. Publication bias was analyzed by using the Begg's and Egger's linear regression test and funnel plots [22]. $P<0.05$ is considered statistically significant.

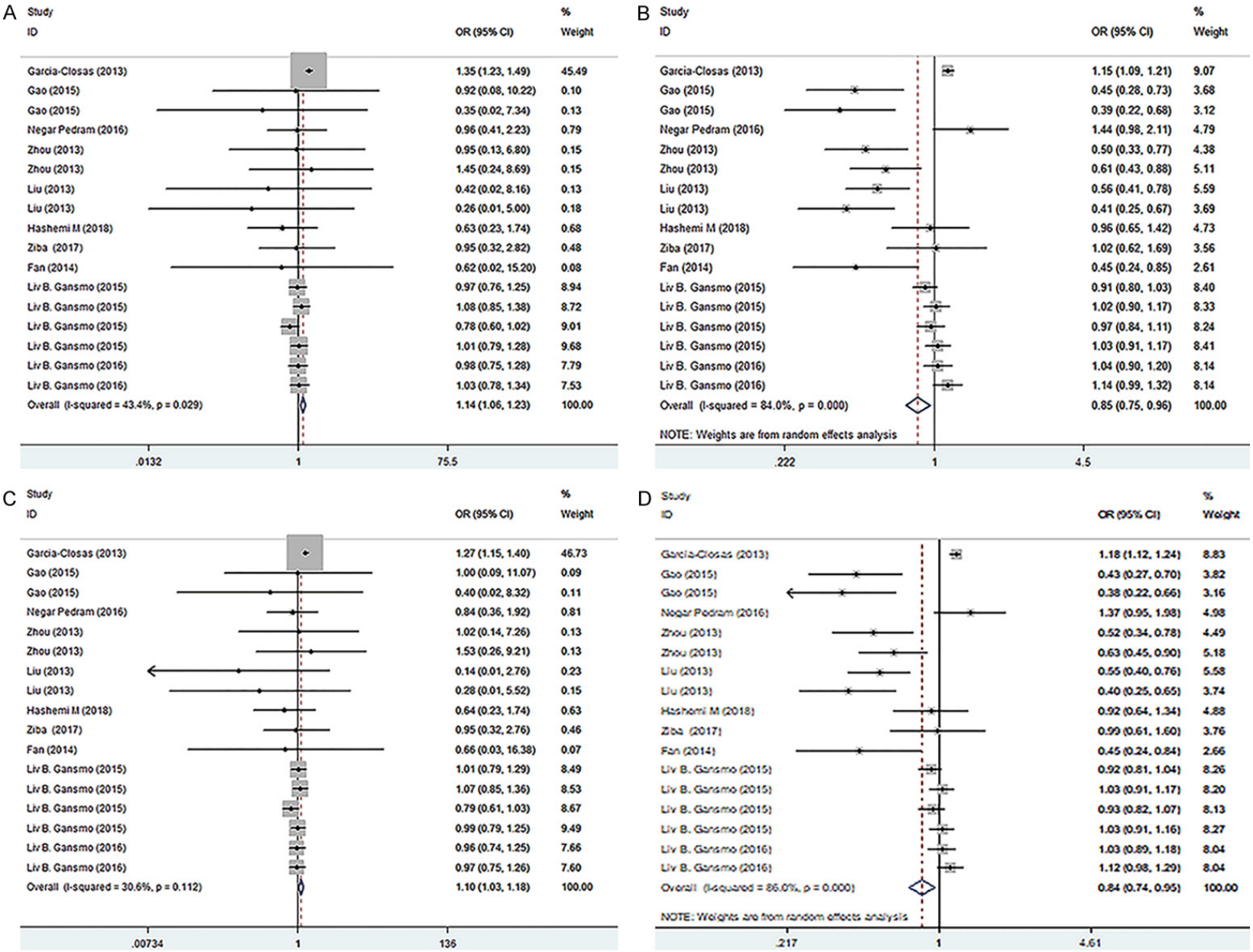
Results

Characteristics of the included publications

Through a systematic literature search of Pubmed, Web of science, China National Knowledge Infrastructure (CNKI), a total of 38 articles were retrieved (**Figure 1**). After reviewing the full text, 28 articles were excluded for the following reasons: repeated studies, not case and control studies, the genotype frequency data was not available, and was not an assessment of the association between the rs4245739 A>C polymorphism and cancer risk. Ultimately, there were only 10 articles with a total of 17 case-control studies that met the inclusion criteria [13, 23-31], which included 19796 cases and 49681 controls. All the genotype frequencies of the rs4245739 polymorphism in the control was consistent with the Hardy-Weinberg equilibrium (HWE).

Meta-analysis

Overall, the results suggest that rs4245739 was significantly associated with a decreased cancer risk in the genetic models (AC vs. AA: OR = 0.85, 95% CI = 0.75-0.96; AC+CC vs. AA: OR = 0.84, 95% CI = 0.74-0.95); (C vs. A: OR = 0.86, 95% CI = 0.78-0.96). (AC vs. AA: OR = 0.85, 95% CI = 0.75-0.96), dominant (AC+CC vs. AA: OR = 0.84, 95% CI = 0.74-0.95), and allele models (C vs. A: OR = 0.86, 95% CI = 0.78-0.96) (**Figure 2**). Next, subgroup analysis was conducted according to ethnicity. The association seems to be more prominent among Asians. However, an increased ESCC (Esophageal Squamous Cell Carcinoma) risk was found in the recessive and homozygous genetic models after stratification of cancer types (CC vs. AC+AA: OR = 1.10, 95% CI = 1.03-1.18); (CC vs. AA: OR = 1.14, 95% CI = 1.06-1.23) (**Table 2**).


A
Study
ID
OR (95% CI)
%
Weight
Garcia-Closas (2013) 1.35 (1.23, 1.49) 45.49
Gao (2015) 0.92 (0.08, 10.22) 0.10
Gao (2015) 0.35 (0.02, 7.34) 0.13
Negar Pedram (2016) 0.96 (0.41, 2.23) 0.79
Zhou (2013) 0.95 (0.13, 6.80) 0.15
Zhou (2013) 1.45 (0.24, 8.69) 0.15
Liu (2013) 0.42 (0.02, 8.16) 0.13
Liu (2013) 0.26 (0.01, 5.00) 0.18
Hashemi M (2018) 0.63 (0.23, 1.74) 0.68
Ziba (2017) 0.95 (0.32, 2.82) 0.48
Fan (2014) 0.62 (0.02, 15.20) 0.08
Liv B. Gansmo (2015) 0.97 (0.76, 1.25) 8.94
Liv B. Gansmo (2015) 1.08 (0.85, 1.38) 8.72
Liv B. Gansmo (2015) 0.78 (0.60, 1.02) 9.01
Liv B. Gansmo (2015) 1.01 (0.79, 1.28) 9.68
Liv B. Gansmo (2016) 0.98 (0.75, 1.28) 7.79
Liv B. Gansmo (2016) 1.03 (0.78, 1.34) 7.53
Overall (I-squared = 43.4%, p = 0.029) 1.14 (1.06, 1.23) 100.00
.0132
1
75.5
B
Study
ID
OR (95% CI)
%
Weight
Garcia-Closas (2013) 1.15 (1.09, 1.21) 9.07
Gao (2015) 0.45 (0.28, 0.73) 3.68
Gao (2015) 0.39 (0.22, 0.68) 3.12
Negar Pedram (2016) 1.44 (0.98, 2.11) 4.79
Zhou (2013) 0.50 (0.33, 0.77) 4.38
Zhou (2013) 0.61 (0.43, 0.88) 5.11
Liu (2013) 0.56 (0.41, 0.78) 5.59
Liu (2013) 0.41 (0.25, 0.67) 3.69
Hashemi M (2018) 0.96 (0.65, 1.42) 4.73
Ziba (2017) 1.02 (0.62, 1.69) 3.56
Fan (2014) 0.45 (0.24, 0.85) 2.61
Liv B. Gansmo (2015) 0.91 (0.80, 1.03) 8.40
Liv B. Gansmo (2015) 1.02 (0.90, 1.17) 8.33
Liv B. Gansmo (2015) 0.97 (0.84, 1.11) 8.24
Liv B. Gansmo (2015) 1.03 (0.91, 1.17) 8.41
Liv B. Gansmo (2016) 1.04 (0.90, 1.20) 8.14
Liv B. Gansmo (2016) 1.14 (0.99, 1.32) 8.14
Overall (I-squared = 84.0%, p = 0.000) 0.85 (0.75, 0.96) 100.00
NOTE: Weights are from random effects analysis
.222
1
4.5
C
Study
ID
OR (95% CI)
%
Weight
Garcia-Closas (2013) 1.27 (1.15, 1.40) 46.73
Gao (2015) 1.00 (0.09, 11.07) 0.09
Gao (2015) 0.40 (0.02, 8.32) 0.11
Negar Pedram (2016) 0.84 (0.36, 1.92) 0.81
Zhou (2013) 1.02 (0.14, 7.26) 0.13
Zhou (2013) 1.53 (0.26, 9.21) 0.13
Liu (2013) 0.14 (0.01, 2.76) 0.23
Liu (2013) 0.28 (0.01, 5.52) 0.15
Hashemi M (2018) 0.64 (0.23, 1.74) 0.63
Ziba (2017) 0.95 (0.32, 2.76) 0.46
Fan (2014) 0.66 (0.03, 16.38) 0.07
Liv B. Gansmo (2015) 1.01 (0.79, 1.29) 8.49
Liv B. Gansmo (2015) 1.07 (0.85, 1.36) 8.53
Liv B. Gansmo (2015) 0.79 (0.61, 1.03) 8.67
Liv B. Gansmo (2015) 0.99 (0.79, 1.25) 9.49
Liv B. Gansmo (2016) 0.96 (0.74, 1.25) 7.66
Liv B. Gansmo (2016) 0.97 (0.75, 1.26) 7.60
Overall (I-squared = 30.6%, p = 0.112) 1.10 (1.03, 1.18) 100.00
.00734
1
136
D
Study
ID
OR (95% CI)
%
Weight
Garcia-Closas (2013) 1.18 (1.12, 1.24) 8.83
Gao (2015) 0.43 (0.27, 0.70) 3.82
Gao (2015) 0.38 (0.22, 0.66) 3.16
Negar Pedram (2016) 1.37 (0.95, 1.98) 4.98
Zhou (2013) 0.52 (0.34, 0.78) 4.49
Zhou (2013) 0.63 (0.45, 0.90) 5.18
Liu (2013) 0.55 (0.40, 0.76) 5.58
Liu (2013) 0.40 (0.25, 0.65) 3.74
Hashemi M (2018) 0.92 (0.64, 1.34) 4.88
Ziba (2017) 0.99 (0.61, 1.60) 3.76
Fan (2014) 0.45 (0.24, 0.84) 2.66
Liv B. Gansmo (2015) 0.92 (0.81, 1.04) 8.26
Liv B. Gansmo (2015) 1.03 (0.91, 1.17) 8.20
Liv B. Gansmo (2015) 0.93 (0.82, 1.07) 8.13
Liv B. Gansmo (2015) 1.03 (0.91, 1.16) 8.27
Liv B. Gansmo (2016) 1.03 (0.89, 1.18) 8.04
Liv B. Gansmo (2016) 1.12 (0.98, 1.29) 8.04
Overall (I-squared = 86.0%, p = 0.000) 0.84 (0.74, 0.95) 100.00
NOTE: Weights are from random effects analysis
.217
1
4.61

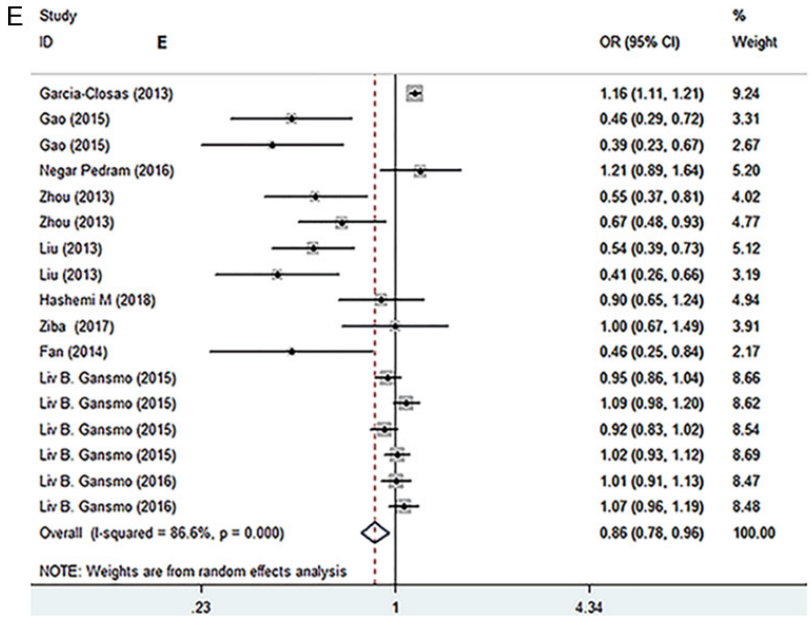


Figure 2. Forest plots for association between five genetic models of rs4245739 and cancer risk. A. Represents Homozygous (CC vs. AA); B. Represents Heterozygote (AC vs. AA); C. Represents Recessive (CC vs. AC+AA); D. Represents Dominant (AC+CC vs. AA); E. Represents Allele (C vs. A).

Table 2. The result of meta-analysis for associations between the rs4245739 polymorphism and cancer risk

Variables	No. of studies	Homozygous CC vs. AA			Heterozygote AC vs. AA			Recessive CC vs. AC+AA			Dominant AC+CC vs. AA			Allele C vs. A		
		OR (95% CI)	P^h	I^2 (%)	OR (95% CI)	P^h	I^2 (%)	OR (95% CI)	P^h	I^2 (%)	OR (95% CI)	P^h	I^2 (%)	OR (95% CI)	P^h	I^2 (%)
Overall	17	1.14 (1.06, 1.23)	<0.05	43.4%	0.85 (0.75, 0.96)	0.008	84.0%	1.10 (1.03, 1.18)	0.006	30.6%	0.84 (0.74, 0.95)	0.005	86.0%	0.86 (0.78, 0.96)	0.005	86.6%
Cancer type																
Breast	6	0.93 (0.62, 1.41)	0.744	73.0%	0.88 (0.68, 1.12)	0.308	87.6%	0.90 (0.61, 1.31)	0.578	69.5%	0.86 (0.67, 1.11)	0.274	89.9%	0.85 (0.67, 1.06)	0.148	91.1%
Lung	3	1.07 (0.84, 1.37)	0.599	0.0%	0.58 (0.29, 1.19)	0.136	90.0%	1.07 (0.84, 1.35)	0.588	0.0%	0.57 (0.27, 1.20)	0.139	91.2%	0.60 (0.28, 1.27)	0.181	92.2%
ESCC	2	1.20 (0.32, 4.50)	0.790	0.0%	0.56 (0.43, 0.74)	<0.05	0.00%	1.27 (0.34, 4.78)	0.721	0.0%	0.58 (0.44, 0.76)	<0.05	0.0%	0.62 (0.48, 0.97)	<0.05	0.0%
Others	6	0.99 (0.88, 1.13)	0.923	0.0%	1.00 (0.89, 1.12)	0.996	57.7%	0.98 (0.87, 1.11)	0.789	0.0%	1.00 (0.89, 1.11)	0.946	55.5%	1.00 (0.92, 1.08)	0.940	44.7%
Ethnicity																
Asian	10	0.82 (0.51, 1.32)	0.414	0.0%	0.63 (0.48, 0.83)	0.001	75.1%	0.78 (0.49, 1.25)	0.301	0.0%	0.62 (0.47, 0.81)	0.001	75.1%	0.63 (0.49, 0.81)	<0.05	75.6%
Caucasian	7	1.03 (0.88, 1.22)	0.695	75.3%	1.04 (0.97, 1.12)	0.275	63.1%	1.02 (0.89, 1.17)	0.768	66.6%	1.04 (0.95, 1.13)	0.389	75.1%	1.03 (0.96, 1.11)	0.398	79.9%

Publication bias and Sensitivity analysis

Figure 3 has the funnel plots of the meta-analysis. It can be seen that the funnel plots are asymmetrical, and the *P* values of the five models of the Egger's test are all <0.05, indicating that there is a publication bias in this study. We also performed a sensitivity analysis by excluding each study once in every genetic model for rs4245739. The results show that no individual study had an impact on the stability of the overall results. Which means the crude OR and 95% CI about the strength of the association between the five models of MDM4 rs4245739 A>C polymorphism and overall cancer risk are credible (**Table 3**).

Discussion

P53, a tumor suppressor protein commonly found in human cancers, is also named "the guardian of the genome" [32]. The P53 pathway is mainly regulated by mouse double-minute protein 2 (MDM2) and protein p14ARF, in which MDM2 is proteasome-degraded against p53, while p14ARF increases p53 levels by inhibiting MDM2 [33, 34]. Thus, MDM2 is a key regulator of the inhibition of P53 activity. MDM4 is a homologous protein of MDM2, it can synergize with MDM2 to inhibit P53 activity and contribute to tumor development and progression.

Many previous studies have shown that genetic polymorphism rs4245739 A>C of the MDM4 gene is closely related to tumor risk. Jin [35], Wang [36], Zhai [37], and Xu [38] et al have evaluated the relationship between genetic polymorphism rs4245739 A>C and cancer risk through a meta-analysis of previous studies. As a data update, the current meta-analysis adds two new studies including a total of 19796 cases and 49681 controls. Our findings are basically consistent with previous studies, indicating that this SNP was significantly associated with a decreased overall cancer risk in the heterozygous, dominant, and allele models. The reason why SNP rs4245739 A>C affects cancer risk may be due to its effect on MDM4 mRNA stability and protein levels, as it creates a target site for hsa-miR-191, leading to a decrease in MDM4 mRNA level [39]. The reduction in MDM4 expression reduces the inhibition of P53 activity, thereby reducing the risk of cancer.

The opposite results were found in subgroup analysis by cancer types; a significant association between MDM4 rs4245739 polymorphism and increased ESCC cancer risk was detected under recessive and homozygous genetic models, but not with breast cancer, lung cancer, and other types of cancer, which may be associated with the expression levels of hsa-miR-191 being different in different cancer types and the heterogeneity of different cancer types. We also performed a subgroup analysis in different ethnicities, the association seems to be more prominent among Asians, this may be due to genotype frequencies being different among different races.

However, this meta-analysis has some limitations. First, we cannot ignore the heterogeneity. The heterogeneity may be due to differences in different races and cancer types. Secondly, our research also has a publication bias. This may be due to the fact that newly published articles have not been included, and there are still some articles lacking the genotype data of the control group. Again, due to the limitations of the original data, we cannot make statistical analysis of the interaction between genes and the environment. Finally, in the subgroup analysis, the number of studies for different cancer types was small, and we were unable to conduct a stratified analysis of all different cancer types, and the meta-analysis only involved Asians and Caucasians.

In conclusion, our meta-analysis results suggest that MDM4 rs4245739 polymorphism was associated with a significantly decreased risk of cancer, especially in Asian populations. However, an increased risk of cancer was observed in ESCC. Considering the limitations of the current meta-analysis, larger scale case-control studies with different races and different cancer types should be further developed to reach a comprehensive conclusion.

Disclosure of conflict of interest

None.

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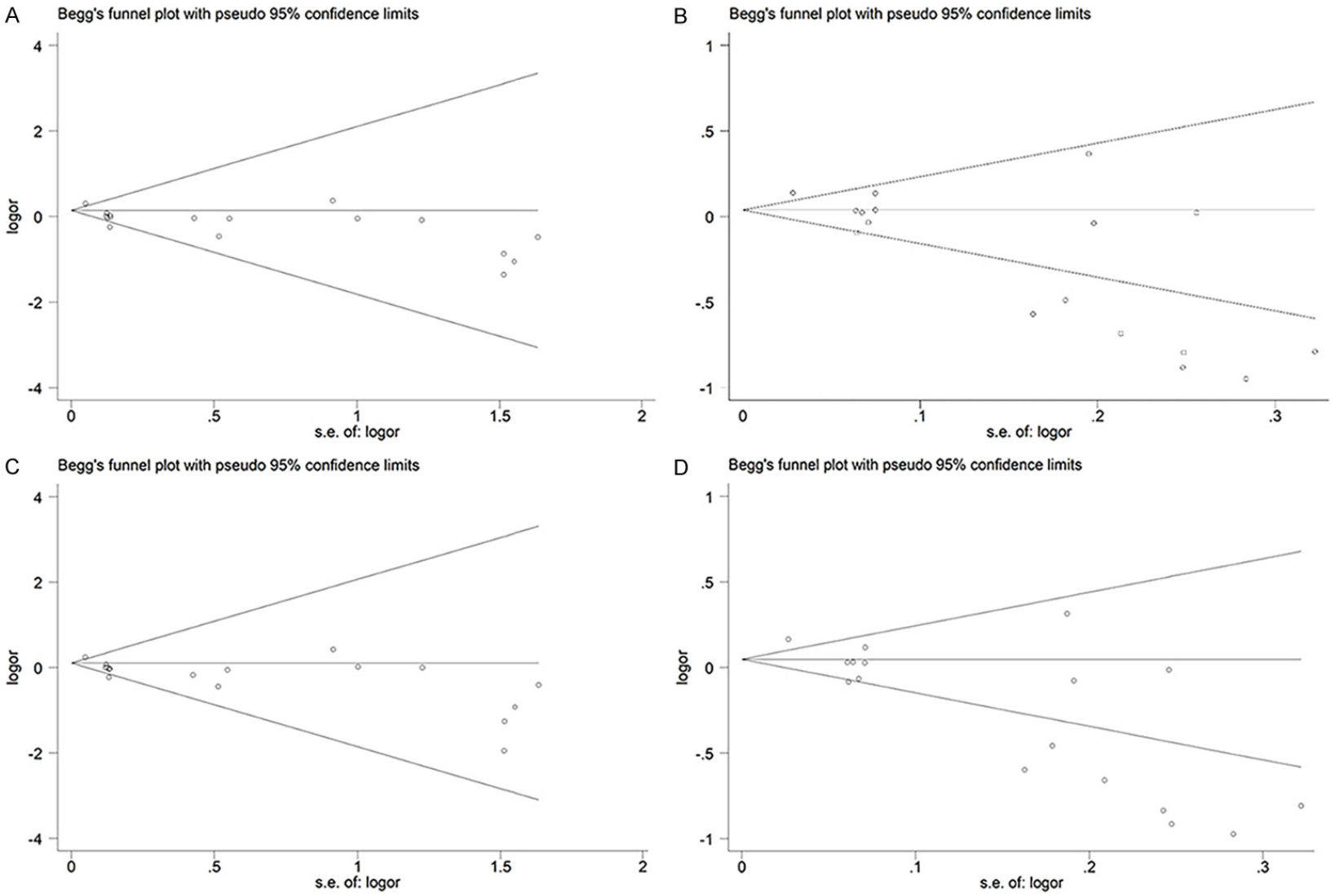
A
Begg's funnel plot with pseudo 95% confidence limits
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Begg's funnel plot with pseudo 95% confidence limits
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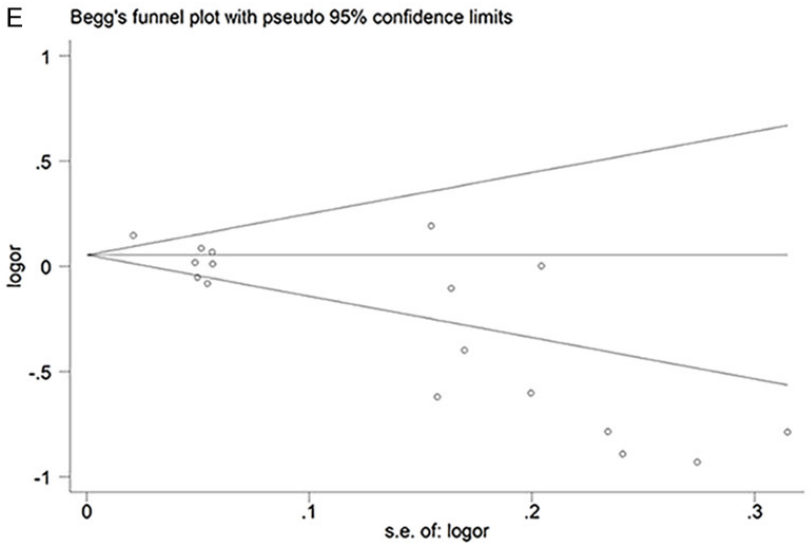

Figure 3. Funnel plots of five genetic models. A. Represents Homozygous (CC vs. AA); B. Represents Heterozygote (AC vs. AA); C. Represents Recessive (CC vs. AC+AA); D. Represents Dominant (AC+CC vs. AA); E. Represents Allele (C vs. A).

Table 3. Sensitivity analysis

Study omitted	Cases/controls (n)	Crude OR 95% CI				
		Homozygous CC vs. AA	Heterozgous AC vs. AA	Recessive CC vs. AC+AA	Dominant AC+CC vs. AA	Allele C vs. A
Closas [24]	6512/41451	0.96 (0.87, 1.07)	0.82 (0.72, 0.94)	0.96 (0.87, 1.05)	0.81 (0.71, 0.92)	0.83 (0.75, 0.93)
Gao [31]	320/640	1.14 (1.06, 1.23)	0.88 (0.78, 0.99)	1.10 (1.03, 1.18)	0.87 (0.77, 0.98)	0.89 (0.80, 0.98)
Gao [31]	200/400	1.14 (1.06, 1.23)	0.88 (0.78, 0.99)	1.10 (1.03, 1.18)	0.87 (0.77, 0.98)	0.89 (0.80, 0.98)
Pedram N [30]	220/260	1.14 (1.06, 1.23)	0.83 (0.73, 0.94)	1.10 (1.03, 1.18)	0.82 (0.72, 0.93)	0.84 (0.76, 0.94)
Zhou [27]	540/550	1.14 (1.06, 1.23)	0.88 (0.78, 0.99)	1.10 (1.03, 1.18)	0.86 (0.77, 0.97)	0.88 (0.80, 0.98)
Zhou [27]	588/600	1.14 (1.06, 1.23)	0.87 (0.77, 0.98)	1.10 (1.03, 1.18)	0.86 (0.76, 0.97)	0.87 (0.79, 0.97)
Liu [29]	800/800	1.14 (1.06, 1.23)	0.88 (0.78, 0.99)	1.10 (1.03, 1.18)	0.87 (0.77, 0.98)	0.89 (0.81, 0.99)
Liu [29]	300/600	1.14 (1.06, 1.23)	0.88 (0.78, 0.99)	1.10 (1.03, 1.18)	0.87 (0.77, 0.98)	0.89 (0.89, 0.98)
Hashemi [28]	265/221	1.15 (1.07, 1.23)	0.84 (0.74, 0.96)	1.11 (1.03, 1.18)	0.83 (0.73, 0.95)	0.86 (0.77, 0.96)
Ziba [26]	102/232	1.14 (1.06, 1.23)	0.84 (0.75, 0.95)	1.10 (1.03, 1.18)	0.83 (0.73, 0.94)	0.86 (0.77, 0.95)
Fan [25]	200/400	1.14 (1.06, 1.23)	0.87 (0.77, 0.98)	1.10 (1.03, 1.18)	0.86 (0.76, 0.97)	0.88 (0.79, 0.97)
Gansmo [13]	2500/1877	1.16 (1.08, 1.25)	0.84 (0.74, 0.96)	1.11 (1.03, 1.19)	0.83 (0.72, 0.94)	0.85 (0.76, 0.95)
Gansmo [13]	1331/3747	1.15 (1.07, 1.24)	0.83 (0.73, 0.95)	1.10 (1.03, 1.19)	0.82 (0.71, 0.93)	0.83 (0.74, 0.94)
Gansmo [13]	1717/1870	1.18 (1.09, 1.27)	0.83 (0.73, 0.95)	1.13 (1.05, 1.22)	0.83 (0.72, 0.94)	0.86 (0.76, 0.95)
Gansmo [13]	1531/3747	1.16 (1.07, 1.25)	0.83 (0.72, 0.95)	1.11 (1.04, 1.20)	0.82 (0.71, 0.93)	0.84 (0.75, 0.94)
Gansmo [23]	1404/2050	1.16 (1.07, 1.24)	0.83 (0.73, 0.95)	1.11 (1.04, 1.20)	0.82 (0.72, 0.94)	0.84 (0.75, 0.94)
Gansmo [23]	1367/2050	1.15 (1.07, 1.24)	0.82 (0.72, 0.94)	1.11 (1.04, 1.20)	0.81 (0.71, 0.93)	0.84 (0.75, 0.94)

References

[1] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018; 68: 7-30.

[2] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.

[3] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015; 65: 5-29.

[4] Ponder BA. Cancer genetics. Nature 2001; 411: 336-341.

[5] Shvarts A, Steegenga WT, Riteco N, van Laar T, Dekker P, Bazuine M, van Ham RC, van der Houven van Oordt W, Hateboer G, van der Eb AJ and Jochemsen AG. MDMX: a novel p53-binding protein with some functional properties of MDM2. EMBO J 1996; 15: 5349-5357.

[6] Wade M, Wang YV and Wahl GM. The p53 orchestra: Mdm2 and Mdmx set the tone. Trends Cell Biol 2010; 20: 299-309.

[7] Kadakia M, Brown TL, McGorry MM and Berberich SJ. MdmX inhibits Smad transactivation. Oncogene 2002; 21: 8776-8785.

[8] Jin Y, Zeng SX, Sun XX, Lee H, Blattner C, Xiao Z and Lu H. MDMX promotes proteasomal turnover of p21 at G1 and early S phases independently of, but in cooperation with, MDM2. Mol Cell Biol 2008; 28: 1218-1229.

[9] Miller KR, Kelley K, Tuttle R and Berberich SJ. HdmX overexpression inhibits oncogene induced cellular senescence. Cell Cycle 2010; 9: 3376-3382.

[10] Levine AJ. p53, the cellular gatekeeper for growth and division. Cell 1997; 88: 323-331.

[11] Harris SL and Levine AJ. The p53 pathway: positive and negative feedback loops. Oncogene 2005; 24: 2899-2908.

[12] Junttila MR and Evan GI. p53--a Jack of all trades but master of none. Nat Rev Cancer 2009; 9: 821-829.

[13] Gansmo LB, Romundstad P, Birkeland E, Hveem K, Vatten L, Knappskog S and Lonning PE. MDM4 SNP34091 (rs4245739) and its effect on breast-, colon-, lung-, and prostate cancer risk. Cancer Med 2015; 4: 1901-1907.

[14] Valentin-Vega YA, Barboza JA, Chau GP, El-Naggar AK and Lozano G. High levels of the p53 inhibitor MDM4 in head and neck squamous carcinomas. Hum Pathol 2007; 38: 1553-1562.

[15] Danovi D, Meulmeester E, Pasini D, Migliorini D, Capra M, Frenk R, de Graaf P, Francoz S, Gasparini P, Gobbi A, Helin K, Pelicci PG, Jochemsen AG and Marine JC. Amplification of Mdmx (or Mdm4) directly contributes to tumor formation by inhibiting p53 tumor suppressor activity. Mol Cell Biol 2004; 24: 5835-5843.

[16] Laurie NA, Donovan SL, Shih CS, Zhang J, Mills N, Fuller C, Teunisse A, Lam S, Ramos Y, Mohan A, Johnson D, Wilson M, Rodriguez-Galindo C, Quarto M, Francoz S, Mendrysa SM, Guy RK, Marine JC, Jochemsen AG and Dyer MA. Inactivation of the p53 pathway in retinoblastoma. Nature 2006; 444: 61-66.

[17] Han X, Garcia-Manero G, McDonnell TJ, Lozano G, Medeiros LJ, Xiao L, Rosner G, Nguyen M, Fernandez M, Valentin-Vega YA, Barboza J, Jones DM, Rassidakis GZ, Kantarjian HM and Bueso-Ramos CE. HDM4 (HDMX) is widely expressed in adult pre-B acute lymphoblastic leukemia and is a potential therapeutic target. Mod Pathol 2007; 20: 54-62.

[18] Wasylishen AR and Lozano G. Attenuating the p53 pathway in human cancers: many means to the same end. Cold Spring Harb Perspect Med 2016; 6.

[19] Stegeman S, Moya L, Selth LA, Spurdle AB, Clements JA and Batra J. A genetic variant of MDM4 influences regulation by multiple microRNAs in prostate cancer. Endocr Relat Cancer 2015; 22: 265-276.

[20] DerSimonian R and Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015; 45: 139-145.

[21] Mantel N and Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-748.

[22] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.

[23] Gansmo LB, Bjornslett M, Halle MK, Salvesen HB, Dorum A, Birkeland E, Hveem K, Romundstad P, Vatten L, Lonning PE and Knappskog S. The MDM4 SNP34091 (rs4245739) C-allele is associated with increased risk of ovarian-but not endometrial cancer. Tumour Biol 2016; 37: 10697-10702.

[24] Garcia-Closas M, Couch FJ, Lindstrom S, Michailidou K, Schmidt MK, Brook MN, Orr N, Rhie SK, Riboli E, Feigelson HS, Le Marchand L, Buring JE, Eccles D, Miron P, Fasching PA, Brauch H, Chang-Claude J, Carpenter J, Godwin AK, Nevanlinna H, Giles GG, Cox A, Hopper JL, Bolla MK, Wang Q, Dennis J, Dicks E, Howat WJ, Schoof N, Bojesen SE, Lambrechts D, Broeks A, Andrulis IL, Guenel P, Burwinkel B, Sawyer EJ, Hollestelle A, Fletcher O, Winqvist R, Brenner H, Mannermaa A, Hamann U, Meindl A, Lindblom A, Zheng W, Devillee P, Goldberg MS, Lubinski J, Kristensen V, Swerdlow A, Anton-Culver H, Dork T, Muir K, Matsuo K, Wu AH, Radice P, Teo SH, Shu XO, Blot W, Kang D, Hartman M, Sangrajrang S, Shen CY, Southey MC, Park DJ, Hammet F, Stone J, Veer LJ, Rutgers EJ, Lophatananon A, Stewart-Brown S, Siriwanarangsan P, Peto J, Schrauder MG, Ekici AB, Beckmann MW, Dos Santos Silva I, Johnson N, Warren H, Tomlinson I, Kerin MJ, Miller N, Marme F, Schneeweiss A, Sohn C, Truong T, Laurent-Puig P, Kerbrat P, Nordestgaard BG, Nielsen SF, Flyger H, Milne RL, Perez JI, Menendez P, Muller H, Arndt V, Stegmaier C, Lichtner P, Lochmann M, Justenhoven C, Ko YD, Muranen TA, Aittomaki K, Blomqvist C, Greco D, Heikkinen T, Ito H, Iwata H, Yatabe Y, Antonenkova NN, Margolin S, Kataja V, Kosma VM, Hartikainen JM, Balleine R, Tseng CC, Berg DV, Stram DO, Neven P, Dieudonne AS, Leunen K, Rudolph A, Nickels S, Flesch-Janys D, Peterlongo P, Peissel B, Bernard L, Olson JE, Wang X, Stevens K, Severi G, Baglietto L, McLean C, Coetzee GA, Feng Y, Henderson BE, Schumacher F, Bogdanova NV, Labreche F, Dumont M, Yip CH, Taib NA, Cheng CY, Shrubsole M, Long J, Pylkas K, Jukkola-Vuorinen A, Kauppila S, Knight JA, Glendon G, Mulligan AM, Tollenaar RA, Seynaeve CM, Kriege M, Hooning MJ, van den Ouweland AM, van Deurzen CH, Lu W, Gao YT, Cai H, Balasubramanian SP, Cross SS, Reed MW, Signorello L, Cai Q, Shah M, Miao H, Chan CW, Chia KS, Jakubowska A, Jaworska K, Durda K, Hsiung CN, Wu PE, Yu JC, Ashworth A, Jones M, Tessier DC, Gonzalez-Neira A, Pita G, Alonso MR, Vincent D, Bacot F, Ambrosone CB, Bandera EV, John EM, Chen GK, Hu JJ, Rodriguez-Gil JL, Bernstein L, Press MF, Ziegler RG, Millikan RM, Deming-Halverson SL, Nyante S, Ingles SA, Waisfisz Q, Tsimiklis H, Makalic E, Schmidt D, Bui M, Gibson L, Muller-Myhsok B, Schmutzler RK, Hein R, Dahmen N, Beckmann L, Aaltonen K, Czene K, Irwanto A, Liu J, Turnbull C, Rahman N, Meijers-Heijboer H, Uitterlinden AG, Rivadeneira F, Olswold C, Slager S, Pilarski R, Ademuyiwa F, Konstantopoulou I, Martin NG, Montgomery GW, Slamon DJ, Rauh C, Lux MP, Jud SM, Bruning T, Weaver J, Sharma P, Pathak H, Tapper W, Gerty S, Durcan L, Trichopoulos D, Tumino R, Peeters PH, Kaaks R, Campa D, Canzian F, Weiderpass E, Johansson M, Khaw KT, Travis R, Clavel-Chapelon F, Kolonel LN, Chen C, Beck A, Hankinson SE, Berg CD, Hoover RN, Lissowska J, Figueroa JD, Chasman DI, Gaudet MM, Diver WR, Willett WC, Hunter DJ, Simard J, Benitez J, Dunning AM, Sherman ME, Chenevix-Trench G, Chanock SJ, Hall P, Pharoah PD, Vachon C, Easton DF, Haiman CA and Kraft P. Genome-wide association studies identify four ER negative-specific breast cancer risk loci. Nat Genet 2013; 45: 392-398, 398e391-392.

[25] Fan C, Wei J, Yuan C, Wang X, Jiang C, Zhou C and Yang M. The functional TP53 rs1042522 and MDM4 rs4245739 genetic variants contribute to Non-Hodgkin lymphoma risk. PLoS One 2014; 9: e107047.

[26] Mohammad Khanlou Z, Pouladi N, Hosseinpour Feizi M and Pedram N. Lack of associations of the MDM4 rs4245739 polymorphism with risk of thyroid cancer among Iranian-Azeri patients:

a case-control study. Asian Pac J Cancer Prev 2017; 18: 1133-1138.
[27] Zhou L, Zhang X, Li Z, Zhou C, Li M, Tang X, Lu C, Li H, Yuan Q and Yang M. Association of a genetic variation in a miR-191 binding site in MDM4 with risk of esophageal squamous cell carcinoma. PLoS One 2013; 8: e64331.
[28] Hashemi M, Sanaei S, Hashemi SM, Eskandari E and Bahari G. Association of single nucleotide polymorphisms of the MDM4 gene with the susceptibility to breast cancer in a southeast Iranian population sample. Clin Breast Cancer 2018; 18: e883-e891.
[29] Liu J, Tang X, Li M, Lu C, Shi J, Zhou L, Yuan Q and Yang M. Functional MDM4 rs4245739 genetic variant, alone and in combination with P53 Arg72Pro polymorphism, contributes to breast cancer susceptibility. Breast Cancer Res Treat 2013; 140: 151-157.
[30] Pedram N, Pouladi N, Feizi MA, Montazeri V, Sakhinia E and Estiar MA. Analysis of the association between MDM4 rs4245739 single nucleotide polymorphism and breast cancer susceptibility. Clin Lab 2016; 62: 1303-1308.
[31] Gao F, Xiong X, Pan W, Yang X, Zhou C, Yuan Q, Zhou L and Yang M. A regulatory MDM4 genetic variant locating in the binding sequence of multiple microRNAs contributes to susceptibility of small cell lung cancer. PLoS One 2015; 10: e0135647.
[32] Lane DP. Cancer. p53, guardian of the genome. Nature 1992; 358: 15-16.
[33] Lahav G, Rosenfeld N, Sigal A, Geva-Zatorsky N, Levine AJ, Elowitz MB and Alon U. Dynamics of the p53-Mdm2 feedback loop in individual cells. Nat Genet 2004; 36: 147-150.
[34] Brown CJ, Lain S, Verma CS, Fersht AR and Lane DP. Awakening guardian angels: drugging the p53 pathway. Nat Rev Cancer 2009; 9: 862-873.
[35] Jin X, Zhao W, Zheng M, Zhou P and Niu T. The role of MDM4 SNP34091 A>C polymorphism in cancer: a meta-analysis on 19,328 patients and 51,058 controls. Int J Biol Markers 2017; 32: e62-e67.
[36] Wang MJ, Luo YJ, Shi ZY, Xu XL, Yao GL, Liu RP and Zhao H. The associations between MDM4 gene polymorphisms and cancer risk. Oncotarget 2016; 7: 55611-55623.
[37] Zhai Y, Dai Z, He H, Gao F, Yang L, Dong Y and Lu J. A PRISMA-compliant meta-analysis of MDM4 genetic variants and cancer susceptibility. Oncotarget 2016; 7: 73935-73944.
[38] Xu C, Zhu J, Fu W, Liang Z, Song S, Zhao Y, Lyu L, Zhang A, He J and Duan P. MDM4 rs4245739 A>C polymorphism correlates with reduced overall cancer risk in a meta-analysis of 69477 subjects. Oncotarget 2016; 7: 71718-71726.
[39] Song CG, Fu FM, Wu XY, Wang C and Shao ZM. [Correlation of polymorphism rs1563828 in MDM4 gene with breast cancer risk and onset age]. Zhonghua Wai Ke Za Zhi 2012; 50: 53-56.