The Correlation of Mouse Double Minute 4 (MDM4) Polymorphisms (rs4245739, rs1563828, rs11801299, rs10900598, and rs1380576) with Cancer Susceptibility: A Meta-Analysis

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Background: Mouse double minute 4 (MDM4) has been extensively investigated as a negative regulator of P53, its negative feedback loop, and the effect of its genetic polymorphisms on cancers. However, many studies showed varying and even conflicting results. Therefore, we employed meta-analysis to further assess the intensity of the connection between MDM4 polymorphisms and malignancies.

Material/Methods: We searched eligible articles in 5 databases (Cochrane Library, PubMed, Web of Science, Wan Fang Database, and China National Knowledge Infrastructure) up to August 2021. Odds ratios (ORs) and 95% confidence intervals (CIs) were utilized to probe the correlation of 5 MDM4 polymorphisms (rs4245739, rs1563828, rs11801299, rs10900598, and rs1380576) with carcinomas. We employed meta-regression and subgroup analysis to probe for sources of heterogeneity; Funnel plots, Begg’s test, and Egger’s test were used to evaluate publication bias. Sensitivity analysis was applied to assess the stability of the study.

Results: Twenty-two studies, comprising 77 reports with 29,853 cases and 72,045 controls, were included in our meta-analysis. We found that rs4245739 polymorphism was a factor in reducing overall cancer susceptibility (dominant model, OR=0.85, 95% CI=0.76-0.95; heterozygous model, OR=0.86, 95% CI=0.78-0.96; additive model, OR=0.87, 95% CI=0.79-0.95), especially in Asian populations, and it also reduces the risk for esophageal squamous cell carcinoma (ESCC). The remaining 4 SNPs were not associated with cancers.

Conclusions: The rs4245739 polymorphism might reduce the risk of malignancies, especially in Asian populations, and it is a risk-reducing factor for ESCC incidence. However, rs1563828, rs11801299, rs10900598, and rs1380576 are not relevant to cancer susceptibility.

Keywords: Breast Neoplasms • MDM4 Protein, Human • Meta-Analysis • Polymorphism, Single Nucleotide

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/935671
Background

According to the World Health Organization (WHO), cancer causes a tremendous burden worldwide, in both men and women, second in severity only to ischemic heart disease and stroke. Over the next 40 years, cancer will become the primary cause of death by replacing ischemic heart disease, according to WHO prediction model [1]. Studies on the oncogenesis and therapy of malignancies are urgently required. The occurrence of cancer is due to multiple factors, including alcohol consumption, smoking, obesity, and working and living environment. In addition, hereditary elements, such as single-nucleotide polymorphisms (SNPs), may contribute to the pathogenesis of cancer, as suggested by molecular epidemiological studies [2,3].

Mutation of anti-oncogene has been recognized as an essential factor in cancer genesis and progression. Mutations in the TP53 gene, an anti-oncogene found on chromosome 17p13 and coding for the p53 protein, commonly occur in human carcinomas, leading to p53 loss of activity, which results in tumor initiation and progression [4,5]. Inactivation of p53 tumor suppressor is essential for oncogenesis, and almost all cancers have p53 abnormalities. MDM2/MDM4 functions as a negative regulator for p53 and tightly regulates the activity of p53 [6]. MDM4 is named for its structural similarity to MDM2 and forms a family with it [7]. MDM2 and MDMX (also named HDMX and MDM4) proteins show deregulation in many human cancers and perform carcinogenic functions, primarily by the inhibition of tumor suppressor p53 [8]. Moreover, single-nucleotide polymorphisms in MDM4 may increase or decrease the activity of MDM4 proteins, thus affecting tumorigenesis and progression.

Since its discovery, MDM4 has been widely studied due to its structural and functional similarity to MDM2, especially focusing on its single-nucleotide polymorphisms in tumors. The associations of rs4245739, rs1563828, rs11801299, rs10900598, and rs1380576 polymorphisms with cancers have been studied more frequently, including breast cancer, gastric cancer, nasopharyngeal cancer (NPC), colorectal cancer, squamous cell carcinoma of the head and neck (SCCHN), lung cancer, esophageal squamous cell carcinoma (ESCC), prostate cancer, endometrial cancer, hereditary melanoma, ovarian cancer, non-Hodgkin lymphoma (NHL), thyroid cancer, retinoblastoma, and acute myeloid leukemia (AML) [9-31]. The association of MDM4 polymorphisms with cancers has been studied based on the references of the included studies.

Material and Methods

This study derived all data from published literature and did not directly involve patients. Therefore, the approval of the ethics committee and informed consent was not a requirement.

Registration Information

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Literature Search

Included in this meta-analysis were studies obtained from 5 databases (Cochrane Library, PubMed, Web of Science, Wan Fang Database, and CNKI) up to August 2021. The search terms on PubMed are shown in Table 1; the terms in the other 4 databases are roughly the same. No language restrictions were used in this search. We also accessed other relevant articles based on the references of the included studies.

Inclusion criteria: (a) Studies for MDM4 gene polymorphisms and cancers (at least 1 of the 5 SNPs). (b) Case-control studies, with the case group having confirmed pathological malignancies. (c) Ability to access complete available data.

Exclusion criteria: (a) Duplicate literature. (b) Non-human experiments. We selected only the most recently published articles or studies with the largest sample sizes when multiple studies had overlapping data.

Two researchers separately performed the search and screening according to the same strategy. In case inconsistencies were found, discussions were held until the results were consistent between the 2 individuals.

Data Extraction

Both investigators separately extracted the following data from the available literature: first author, year of publication, cancer type, country region, ethnicity, control group source, genotyping method, gene frequencies in the case and control groups, and the P value of Hardy-Weinberg equilibrium (HWE). If a study did not mention the P value of HWE, the goodness-of-fit test was used to identify whether the gene frequency distribution of the control groups conformed to HWE; P>0.05
Table 1. Search strategy for PubMed database.

| ("Neoplasms"[Mesh]) OR (Neoplasia[Title/Abstract]) OR (Neoplasms[Title/Abstract]) OR (Neoplasm[Title/Abstract]) OR (Tumors[Title/Abstract]) OR (Tumor[Title/Abstract]) OR (Cancer[Title/Abstract]) OR (Cancers[Title/Abstract]) OR (Malignancy[Title/Abstract]) OR (Malignancies[Title/Abstract]) OR (Malignant Neoplasms[Title/Abstract]) OR (Malignant Neoplasm[Title/Abstract]) OR (Neoplasm, Malignant[Title/Abstract]) OR (Neoplasms, Malignant[Title/Abstract]) AND
| ("MDM4 protein, human" [Supplementary Concept]) OR (MDMX protein, human[Title/Abstract]) OR (Mdm2-like p53-binding protein, human[Title/Abstract]) OR (hMDMX protein, human[Title/Abstract]) OR (Double minute 4 protein, human[Title/Abstract]) OR (Mdm4, transformed 3T3 cell double minute 4, p53 binding protein (mouse) protein, human[Title/Abstract]) OR (Hdmx protein, human[Title/Abstract]) OR (MDM4[Title/Abstract]) OR (rs4245739[Title/Abstract]) OR (rs1563828[Title/Abstract]) OR (rs11801299[Title/Abstract]) OR (rs10900598[Title/Abstract]) OR (rs1380576[Title/Abstract]) AND
| ("polymorphism, single nucleotide"[MeSH]) OR ("Mutation"[Mesh]) OR ("Genetic Variation"[Mesh]) OR ("Alleles"[Mesh]) OR (nucleotide polymorphism single[Title/Abstract]) OR (nucleotide polymorphisms single[Title/Abstract]) OR (polymorphisms single nucleotide[Title/Abstract]) OR (single nucleotide polymorphisms[Title/Abstract]) OR (SNPs[Title/Abstract]) OR (polymorphism single nucleotide[Title/Abstract]) OR (Polymorphism[Title/Abstract]) AND
| ("Case-Control Studies"[Mesh]) OR (Case-Control Study[Publication Type]) OR (StudieS, Case-Control[Publication Type]) OR (Study, Case-Control[Publication Type])

was regarded as consistent with the HWE. Reports that did not conform to HWE were excluded from this meta-analysis. The 2 researchers cross-checked the extracted data to avoid any discrepancies.

Quality Assessment

Two researchers evaluated the quality of the studies included based on the Newcastle-Ottawa Scale (NOS). The case-control trials were scored on 3 dimensions: selection, comparability, and exposure, with a total score of 9. A score of 5~9 was considered high quality, while a score of 0~4 was considered low quality [37]. In case of disagreement between 2 investigators, discussion with a third party was required until agreement was reached.

Statistical Analysis

**Statistical software:** STATA 16.0

**Quantitative synthesis:** The combined ORs and 95% CI were employed to evaluate the association of 5 MDM4 polymorphisms (Y>X) with malignancy in the dominant (XY+YY vs XX), recessive (YY vs XY+XX), heterozygous (XY vs XX), and additive (Y vs X) models. X represents the major allele and Y represents the minor allele. Gene frequencies for all genotypes were derived from included case-control studies, and related studies lacking gene frequencies were eliminated.

**Heterogeneity analysis:** We used Cochran’s Q test and the I² statistic to assess the level of heterogeneity for the original studies. P values of Cochran’s Q test less than 0.05 or I² more significant than 50% were considered significant heterogeneity. In cases of insignificant heterogeneity, fixed-effects models were employed to merge ORs to assess the association of individual models with tumor risk; otherwise, random-effects models were applied. We performed a meta-regression analysis based on publication year, ethnicity, cancer type, genotyping methods, and source of controls to explore the sources of heterogeneity (P value less than 0.05 shows heterogeneity).

**Subgroup analysis:** We performed subgroup analyses of the included studies for ethnicity, cancer type, and control source to further probe sources of heterogeneity and investigate the association of MDM4 polymorphisms with cancer risk.

**Publication bias:** We utilized the contour-enhanced funnel plot, Begg’s test, and Egger’s test to evaluate the publication bias risks. Publication bias was suggested if the funnel plot was asymmetric and/or the P value for Begg’s and Egger’s test was less than 0.05. When publication bias existed, the trim and fill method would be employed to estimate how the bias affected the study outcomes.

**Sensitivity analysis:** When included studies exceeded 10, the leave-one-out method was implemented to evaluate the stability of the results by re-merging the ORs with 95% CIs after excluding individual studies in turn. The results of this meta-analysis were stable if the ORs and CIs were not reversed.
### Results

After systematically searching the 5 significant databases, we initially obtained 324 records. After excluding 40 duplicate records, 284 articles remained. We then closely read titles and abstracts to exclude 255 articles, including 253 irrelevant publications and 2 meta-analyses. We performed a full-text reading of the 29 papers which were left and eliminated 6 papers, 5 of which lacked gene frequencies, and 1 for overlapping data with another study. We also included 1 study that matched the criteria by hand searching. A total of 23 studies were enrolled, including 78 reports, of which 61 were dedicated to studying the link between the rs4245739 polymorphism and cancer risk [10-21,29,30].

The above process can be more intuitively understood from Figure 1.

We obtained 23 studies and extracted relevant data to fill in Table 2. Thirteen articles concentrated on White populations and another 10 on Asian populations; there were no studies on African populations. The article on 3 genome-wide association studies (GWASs) by Garcia-Closaset et al contained 40 case-control studies investigating rs4245739 polymorphism and breast cancer risk for White populations. After recalculating the $P$ values of HWE, we noticed that the gene frequencies of the control group of Florin Tripon’s study on rs4245739 and acute myeloid leukemia were not matched with HWE [31], as well as Mohammad Hashemi’s and Guo-cong Wu’s studies on rs1380576 [15,24]. We did not include these 3 reports in the meta-analysis ($P$ values of HWE can be seen in Table 2).

After performing subgroup analysis of cancer types, we found that this SNP was only related to ESCC risk independent of other cancers (dominant model, OR=0.58, 95% CI=0.44-0.76; heterozygous model, OR=0.56, 95% CI=0.43-0.74; additive model, OR=0.61, 95% CI=0.48-0.79). This SNP was discovered to reduce the risk of tumor development in Asian populations by performing subgroup analysis of ethnicity (dominant model, OR=0.57, 95% CI=0.46-0.70; recessive model, OR=0.72, 95% CI=0.52-0.99; heterozygous model, OR=0.58, 95% CI=0.46-0.71; homozygous model, OR=0.68, 95% CI=0.49-0.95; additive model, OR=0.59, 95% CI=0.48-0.72). For subgroup analyses of control group sources, we discovered that the SNP was associated with neoplasm risk in hospital-based, population-based, and mixed groups (HB: recessive model, OR=0.75, 95% CI=0.58-0.97;
Table 2. Characteristics of the included studies.

| Author      | Year | Cancer-type | Country | Ethnicity | Control source | Genotype method | Case | Control | HWE (Control) |
|-------------|------|-------------|---------|-----------|----------------|----------------|------|----------|---------------|
| Garcia-Closas | 2013 | Breast cancer | Multi-center | Caucasian | Mixed | Illumina array | 3318 | 2637 | 557 | 22825 | 15798 | 2828 | 0.412 |
| JB Liu      | 2013 | Breast cancer | China    | Asian     | PB   | PCR-RFLP     | 733  | 67   | 0   | 686   | 111   | 3   | 0.801 |
| JB Liu      | 2013 | Breast cancer | China    | Asian     | PB   | PCR-RFLP     | 278  | 22   | 0   | 501   | 96    | 3   | 0.782 |
| LQ Zhou     | 2013 | ESCC         | China    | Asian     | PB   | PCR-RFLP     | 501  | 37   | 2   | 478   | 70    | 2   | 0.801 |
| LQ Zhou     | 2013 | ESCC         | China    | Asian     | PB   | PCR-RFLP     | 529  | 56   | 3   | 510   | 88    | 2   | 0.679 |
| CB Fan      | 2013 | ESCC         | China    | Asian     | PB   | PCR-RFLP     | 187  | 13   | 0   | 346   | 53    | 1   | 0.785 |
| JB Feng     | 2014 | Gastric cancer | China    | Asian     | HB   | PCR-RFLP     | 208  | 209  | 51  | 210   | 219   | 64  | 0.845 |
| Gansmo      | 2015 | Breast cancer | Norway   | Caucasian | PB   | LightSNiP assay | 966 | 643 | 108 | 1021 | 703 | 146 | 0.271 |
| Gansmo      | 2015 | Colon cancer | Norway   | Caucasian | PB   | LightSNiP assay | 823 | 600 | 108 | 2042 | 1439 | 266 | 0.848 |
| Gansmo      | 2015 | Lung cancer | Norway   | Caucasian | PB   | LightSNiP assay | 715 | 515 | 101 | 2042 | 1439 | 266 | 0.848 |
| Gansmo      | 2015 | Prostate cancer | Norway | Caucasian | PB   | LightSNiP assay | 1412 | 927 | 161 | 1021 | 736 | 120 | 0.271 |
| F Gao       | 2015 | Lung cancer | China    | Asian     | PB   | PCR-RFLP     | 297  | 22   | 1   | 548   | 90    | 2   | 0.701 |
| F Gao       | 2015 | Lung cancer | China    | Asian     | PB   | PCR-RFLP     | 183  | 17   | 0   | 321   | 77    | 2   | 0.514 |
| Pedram      | 2016 | Breast cancer | Iran     | Caucasian | HB   | T-ARMS-PCR assay | 123 | 87  | 10  | 165   | 81    | 14  | 0.061 |
| Gansmo      | 2016 | Ovarian cancer | Norway  | Caucasian | PB   | LightSNiP assay | 716 | 564 | 105 | 1021 | 703 | 146 | 0.271 |
| Gansmo      | 2016 | Endometrial cancer | Norway | Caucasian | PB   | LightSNiP assay | 757 | 541 | 106 | 1021 | 703 | 146 | 0.271 |
| Khanlou     | 2017 | Thyroid cancer | Iran     | Caucasian | HB   | T-ARMS-PCR assay | 63  | 34   | 5   | 144   | 76    | 12  | 0.893 |
| Hashemi     | 2018 | Breast cancer | Iran     | Caucasian | HB   | T-ARMS-PCR assay | 175 | 83  | 7   | 142   | 70    | 9   | 0.995 |
| Pedram      | 2020 | Breast cancer | Iran     | Caucasian | PB   | T-ARMS-PCR assay | 114 | 82  | 10  | 120   | 68    | 11  | 0.946 |
| DM Zhao     | 2020 | Colorectal cancer | China  | Asian     | HB   | MassARRAY   | 304  | 128 | 11  | 323   | 180   | 25  | 1.000 |
| Kotarac     | 2020 | Prostate cancer | Serbia   | Caucasian | HB   | TaqMan      | 198  | 131 | 23  | 182   | 144   | 31  | 0.890 |
| Tripon      | 2020 | AML          | Romania  | Caucasian | HB   | T-ARMS-PCR assay | 202 | 144 | 57  | 209   | 114   | 83  | <0.001 |
Table 2 continued. Characteristics of the included studies.

| Author | Year | Cancer-type | Country | Ethnicity | Control source | Genotype method | Case | Control | HWE (Control) |
|--------|------|-------------|---------|-----------|----------------|----------------|------|---------|--------------|
| CG Song | 2012 | Breast cancer | China | Asian | HB | MassArray | 53 | 14 | 44 | 14 | 0.802 |
| YW Zhang | 2012 | NPC | China | Asian | PB | RT-PCR | 98 | 90 | 21 | 88 | 22 | 0.998 |
| Thunell | 2014 | Hereditary melanoma | Sweden | Caucasian | PB | RT-PCR | 27 | 2 | 389 | 70 | 0.940 |
| HP Yu | 2011 | SCCHN | America | Caucasian | HB | TaqMan | 487 | 111 | 518 | 455 | 106 | 0.917 |
| HP Yu | 2012 | SCCHN | America | Caucasian | HB | TaqMan | 170 | 43 | 150 | 135 | 36 | 0.798 |
| GC Wu | 2015 | Gastric cancer | China | Asian | HB | TaqMan | 188 | 173 | 212 | 290 | 218 | <0.001 |
| MY Wang | 2017 | Gastric cancer | China | Asian | HB | TaqMan | 487 | 97 | 552 | 485 | 136 | 0.180 |
| Hashemi | 2018 | Breast cancer | Iran | Caucasian | HB | T-ARMS-PCR assay | 86 | 26 | 44 | 142 | 27 | <0.001 |
| FH Yu | 2019 | Retinoblastoma | China | Asian | HB | TaqMan | 77 | 10 | 71 | 59 | 18 | 0.426 |
| HP Yu | 2011 | SCCHN | America | Caucasian | HB | TaqMan | 684 | 40 | 665 | 376 | 38 | 0.229 |
| HP Yu | 2012 | SCCHN | America | Caucasian | HB | TaqMan | 118 | 74 | 202 | 109 | 10 | 0.589 |
| MY Wang | 2017 | Gastric cancer | China | Asian | HB | TaqMan | 380 | 158 | 449 | 532 | 192 | 0.271 |
| Hashemi | 2018 | Breast cancer | Iran | Caucasian | HB | T-ARMS-PCR assay | 183 | 6 | 164 | 50 | 4 | 0.997 |
| FH Yu | 2019 | Retinoblastoma | China | Asian | HB | TaqMan | 39 | 38 | 57 | 64 | 27 | 0.491 |
| HP Yu | 2011 | SCCHN | America | Caucasian | HB | TaqMan | 307 | 223 | 296 | 552 | 231 | 0.677 |
| HP Yu | 2012 | SCCHN | America | Caucasian | HB | TaqMan | 233 | 12 | 93 | 156 | 72 | 0.913 |
| MY Wang | 2017 | Gastric cancer | China | Asian | HB | TaqMan | 547 | 83 | 604 | 462 | 107 | 0.393 |

ESCC – esophageal squamous cell carcinoma; NHL – non-Hodgkin lymphoma; NPC – nasopharyngeal cancer; SCCHN – squamous cell carcinoma of the head and neck; AML – acute myeloid leukemia.
| SNPs       | N      | Dominant model (XY+YY vs XX) | Recessive model (YY vs XX+XY) | Heterozygous model (XY vs XX) | Homozygous model (YY vs XX) | Additive model (Y vs X) |
|------------|--------|------------------------------|------------------------------|-----------------------------|----------------------------|-------------------------|
| rs4245739  | 60     | 0.85 (0.76, 0.95) <0.001/83.9% | 0.96 (0.85, 1.08) 0.038/38.5% | 0.86 (0.78, 0.96) <0.001/81.5% | 0.95 (0.82, 1.10) 0.003/51.7% | 0.87 (0.79, 0.95) <0.001/84.6% |
| rs1380576  | 46     | 0.90 (0.72, 1.13) <0.001/87.9% | 0.90 (0.64, 1.28) 0.008/65.2% | 0.92 (0.74, 1.15) 0.76/85.3% | 0.92 (0.62, 1.36) 0.000/70.8% | 0.72 (0.72, 1.08) 0.000<0.001/89.0% |
| GCC        | 2      | 0.58 (0.44, 0.76) 0.00/0.0% | 1.28 (0.34, 4.76) 0.00/0.0% | 0.56 (0.43, 0.74) 0.48/0.0% | 1.20 (0.32, 4.48) 0.75/0.0% | 0.61 (0.48, 0.79) 0.43/0.0% |
| LC         | 3      | 0.59 (0.29, 1.20) <0.001/90.5% | 1.07 (0.84, 1.35) 0.81/0.0% | 0.58 (0.29, 0.99) <0.001/90.0% | 1.07 (0.84, 1.37) 0.76/0.0% | 0.61 (0.75, 0.81) 0.029/71.9% |
| PC         | 2      | 0.90 (0.81, 1.01) 0.0% | 0.96 (0.77, 1.20) 0.12/0.0% | 0.90 (0.80, 1.01) 0.61/0.0% | 0.92 (0.73, 1.15) 0.27/0.0% | 0.93 (0.85, 1.02) 0.29/0.74% |
| Mixed      | 40     | 0.58 (0.18, 1.25) 0.0% | 0.74 (0.66, 0.86) 1.0% | 0.88 (0.77, 0.92) 0.02/0.0% | 0.73 (0.78, 0.80) 0.0% | 0.89 (0.81, 0.97) 0.18/0.0% |
| rs1380576  | 4      | 0.74 (0.15, 0.32) 0.0% | 0.96 (0.81, 1.13) 0.09/0.0% | 0.79 (0.69, 0.91) 0.97/0.0% | 0.79 (0.69, 0.91) 0.97/0.0% | 0.82 (0.73, 0.92) 0.81/0.0% |
| Ethnicity  |        |                              |                              |                              |                              |                          |
| Asian      |        | 0.57 (0.46, 0.70) 0.008/61.7% | 0.72 (0.52, 0.99) 0.00/0.0% | 0.58 (0.46, 0.71) 0.006/62.8% | 0.68 (0.49, 0.95) 0.833/0.00/0.0% | 0.59 (0.48, 0.72) 0.002/67.9% |
| Caucasian  | 51     | 1.04 (0.96, 1.12) 0.01/64.1% | 0.99 (0.88, 1.13) 0.019/51.7% | 1.04 (0.98, 1.12) 0.02/50.1% | 1.00 (0.86, 1.16) 0.002/62.4% | 1.02 (0.95, 1.09) <0.001/70.5% |
| Source of controls | | 0.75 (0.13, 0.65) 0.0% | 0.75 (0.13, 0.65) 0.0% | 0.75 (0.13, 0.65) 0.0% | 0.75 (0.13, 0.65) 0.0% | 0.75 (0.13, 0.65) 0.0% |
| HB         | 7      | 0.79 (0.79, 0.80) 0.008/71.4% | 0.78 (0.78, 0.80) 0.00/0.0% | 0.79 (0.79, 0.80) 0.008/71.4% | 0.78 (0.78, 0.80) 0.00/0.0% | 0.78 (0.78, 0.80) 0.00/0.0% |
| PC         | 2      | 0.79 (0.69, 0.91) 0.001/82.5% | 0.96 (0.87, 1.06) 0.041/0.0% | 0.79 (0.69, 0.91) 0.001/82.3% | 0.97 (0.87, 1.07) 0.01/0.0% | 0.82 (0.73, 0.92) 0.81/0.0% |
| Other*     | 4      | 0.99 (0.81, 1.21) 0.0% | 0.96 (0.80, 1.16) 0.019/0.0% | 0.81 (0.62, 1.07) 0.045/0.0% | 0.83 (0.62, 1.07) 0.045/0.0% | 0.83 (0.62, 1.07) 0.045/0.0% |
| Ethnicity  |        |                              |                              |                              |                              |                          |
| Asian      | 2      | 0.90 (0.46, 1.50) 0.82/81.7% | 0.74 (0.57, 0.96) 0.00/0.0% | 0.47 (0.16, 1.63) 80.9% | 0.59 (0.59, 1.01) 1.9% | 0.55 (0.55, 1.24) 76.2% |
| Caucasian  | 2      | 1.10 (0.95, 1.12) 0.68/0.0% | 1.05 (0.83, 1.34) 0.04/0.0% | 0.94 (1.28, 9.04) 0.00/0.0% | 1.09 (0.85, 1.41) 0.08/0.0% | 1.07 (0.95, 1.19) 0.73/0.0% |
| rs11801299 | 5      | 1.47 (0.94, 2.30) 0.01/0.0% | 1.75 (0.85, 3.60) <0.001/90.0% | 0.93 (0.93, 1.96) <0.001/88.7% | 2.01 (0.86, 4.71) <0.001/92.0% | 1.41 <0.001/94.9% |
| Ethnicity  |        |                              |                              |                              |                              |                          |
| Asian      | 2      | 1.16 (0.99, 1.37) 0.0% | 1.25 (0.58, 2.69) 0.01/0.0% | 1.19 (1.00, 1.41) 0.02/0.0% | 1.33 (0.65, 2.75) 0.03/0.0% | 1.19 (0.84, 1.70) 0.045/75.1% |
| Caucasian  | 3      | 1.64 (0.68, 3.97) 0.0% | 2.01 (0.73, 3.09) 0.02/0.0% | 1.75 (1.75, 0.01) 0.02/0.0% | 1.75 (0.73, 3.09) 0.02/0.0% | 1.92 (0.70, 3.48) 97.1% |
Table 3 continued. Summary of the association between MDM4 polymorphisms (X>Y*) and cancers.

| SNPs       | N     | Dominant model (XY+YY vs XX) | Recessive model (YY vs XY+XX) | Heterozygous model (XY vs XX) | Homozygous model (YY vs XX) | Additive model (Y vs X) |
|------------|-------|-------------------------------|------------------------------|----------------------------|---------------------------|-------------------------|
|            | OR    | (95% CI)                      | P/I (%)                       | OR                         | (95% CI)                  | P/I (%)                 | OR                        | (95% CI)                  | P/I (%)                 |
| rs10900598 (G>T)                     | 3     | 0.63 (0.31, 1.26)             | <0.001/96.9%                 | 0.48 (0.21, 1.13)          | <0.001/95.0%              | 0.70 (0.40, 1.25)       | <0.001/95.0%              | 0.40 (0.13, 1.18)         | <0.001/96.5%              | 0.66 (0.37, 1.17)         | <0.001/97.7% |
| Ethnicity                                         |       |                               |                              |                            |                           |                         |                           |                           |                         |                           |                           |
| Asian                  | 1.03 (0.87, 1.21) | 0.83 (0.62, 1.12) | 1.07 (0.40, 1.27) | 0.86 (0.63, 1.17) | 0.98 (0.86, 1.12) |
| Caucasian           | 0.48 (0.13, 1.83) | 0.34 (0.04, 2.77) | 0.56 (0.19, 1.61) | 0.25 (0.02, 3.44) | 0.53 (0.16, 1.73) |
| rs1563828 (C>T)       | 3     | 0.93 (0.71, 1.22)             | 0.78 (0.49, 1.23)            | 0.97 (0.73, 1.30)          | 0.77 (0.47, 1.24)         | 0.91 (0.74, 1.12)       | 0.750/2.259/0.00/0.98 |
| Ethnicity                                         |       |                               |                              |                            |                           |                         |                           |                           |                         |                           |                           |
| Asian                  | 0.97 (0.71, 1.33) | 0.86 (0.52, 1.40) | 1.00 (0.72, 1.39) | 0.86 (0.51, 1.45) | 0.95 (0.75, 1.20) |
| Caucasian           | 0.81 (0.46, 1.43) | 0.43 (0.10, 1.82) | 0.89 (0.49, 1.60) | 0.41 (0.10, 1.77) | 0.78 (0.49, 1.24) |

* Bold text indicates meaningful results; # X: major allele, Y: minor allele. BC – breast cancer; ESCC – esophageal squamous cell carcinoma; GCC – gastric cancer and colorectal cancer; LC – lung cancer; PC – prostate cancer, Other* – ovarian cancer, endometrial cancer, thyroid cancer, and non-Hodgkin lymphoma; HB – hospital-based; PB – population-based.

homzygous model, OR=0.73, 95% CI=0.56-0.95; additive model, OR=0.89, 95% CI=0.80-0.99; PB: dominant model, OR=0.79, 95% CI=0.69-0.91; heterozygous model, OR=0.79, 95% CI=0.69-0.91; additive model, OR=0.82, 95% CI=0.73-0.92).

rs1380576 (C>G), rs11801299 (G>A), rs10900598 (G>T) and rs1563828 (C>T)

Meta-analysis revealed that rs1380576 (C>G), rs11801299 (G>A), rs10900598 (G>T), and rs1563828 (C>T) polymorphisms were unrelated to the risk of carcinomas. Through subgroup analysis, the rs1380576 polymorphism was found to reduce the risk of tumors in Asian populations (recessive model, OR=0.74, 95% CI=0.57-0.96).

Heterogeneity Analysis

High heterogeneity was found among the studies of rs4245739, rs11801299, and rs10900598, for which we used random-effects models to combine ORs and performed subgroup analysis.

Meta-regression was performed to explore the origin of the heterogeneity for rs4245739 among publication year, ethnicity, cancer type, genotyping methods, and source of controls, the P value was less than 0.001 for ethnicity only, indicating that heterogeneity was derived from ethnicity (Supplementary Table 2), and we further discovered by subgroup analysis that heterogeneity existed mainly in studies on Asian populations.

Publication Bias

Since only the number of studies with rs4245739 was greater than 10, we performed an evaluation of publication bias for rs4245739.

The publication bias was evaluated for the 5 models of rs4245739 with contour-enhanced funnel plots, and a significant asymmetry was observed in the funnel plots for the dominant, heterozygous, and additive models (Figure 3A-3C). However, the asymmetry resulted from the distribution of studies in areas with statistical significance outside the funnel plot’s white color. This suggests that it is incredibly likely that the asymmetry in funnel plots is caused by factors other than publication bias and, most likely, by heterogeneity, since the 3 models share a significant amount of heterogeneity.

To perform a quantitative assessment of publication bias, we performed Begg’s test and Egger’s test. Results of Begg’s test indicated dominant, heterozygous, and additive models with publication bias. However, Egger’s test showed publication bias for all 5 models (dominant model: P_{begg}=0.032, P_{egger}<0.001; recessive model: P_{begg}=0.526, P_{egger}=0.001; heterozygous model: P_{begg}=0.032, P_{egger}<0.001; homozygous model: P_{begg}=0.487, P_{egger}=0.001; additive model: P_{begg}=0.012, P_{egger}<0.001). Therefore, the publication bias of the 5 models was further evaluated with the trim and fill method, and the findings showed that the outcomes of the 5 models were not reversed after trim...
| Study ID          | OR (95% CI)       | % weight |
|------------------|-------------------|----------|
| Garcia-Ciosas (2013) | 1.18 (1.12, 1.24) | 7.23     |
| JB Liu (2013)    | 0.55 (0.40, 0.76) | 4.51     |
| JB Liu (2013)    | 0.40 (0.25, 0.65) | 2.99     |
| LQ Zhou (2013)   | 0.52 (0.34, 0.78) | 3.61     |
| LQ Zhou (2013)   | 0.63 (0.45, 0.90) | 4.18     |
| CB Fan (2014)    | 0.45 (0.24, 0.84) | 2.12     |
| JB Feng (2014)   | 0.93 (0.72, 1.20) | 5.24     |
| Gansmo (2015)    | 0.93 (0.82, 1.07) | 6.64     |
| Gansmo (2015)    | 1.03 (0.91, 1.16) | 6.75     |
| Gansmo (2015)    | 1.03 (0.91, 1.17) | 6.70     |
| Gansmo (2015)    | 0.92 (0.81, 1.04) | 6.74     |
| F Gao (2015)     | 0.46 (0.29, 0.74) | 3.04     |
| F Gao (2015)     | 0.38 (0.22, 0.66) | 2.53     |
| Pedram (2016)    | 1.37 (0.95, 1.98) | 4.01     |
| Gansmo (2016)    | 1.12 (0.98, 1.29) | 6.56     |
| Gansmo (2016)    | 1.03 (0.89, 1.18) | 6.57     |
| Khanlou (2017)   | 1.01 (0.63, 1.64) | 3.03     |
| Hashemi (2018)   | 0.92 (0.64, 1.34) | 3.93     |
| Pedram (2020)    | 1.23 (0.83, 1.82) | 3.74     |
| DM Zhao (2020)   | 0.72 (0.55, 0.94) | 5.11     |
| Kotarac (2020)   | 0.81 (0.60, 1.09) | 4.77     |
| Overall (1-squared=83.9%, p=0.000) | 0.85 (0.76, 0.95) | 100.00   |

Note: Weights are from random effects analysis

| Study ID          | OR (95% CI)       | % weight |
|------------------|-------------------|----------|
| Garcia-Ciosas (2013) | 1.15 (1.09, 1.21) | 7.49     |
| JB Liu (2013)    | 0.56 (0.41, 0.78) | 4.53     |
| JB Liu (2013)    | 0.41 (0.25, 0.67) | 2.97     |
| LQ Zhou (2013)   | 0.50 (0.33, 0.77) | 3.53     |
| LQ Zhou (2013)   | 0.61 (0.42, 0.88) | 4.13     |
| CB Fan (2014)    | 0.45 (0.24, 0.85) | 2.08     |
| JB Feng (2014)   | 0.96 (0.74, 1.26) | 5.14     |
| Gansmo (2015)    | 0.97 (0.84, 1.11) | 6.77     |
| Gansmo (2015)    | 1.03 (0.91, 1.17) | 6.92     |
| Gansmo (2015)    | 1.02 (0.90, 1.17) | 6.85     |
| Gansmo (2015)    | 0.91 (0.80, 1.03) | 6.91     |
| F Gao (2015)     | 0.45 (0.28, 0.73) | 2.96     |
| F Gao (2015)     | 0.39 (0.22, 0.68) | 2.50     |
| Pedram (2016)    | 1.44 (0.98, 2.11) | 3.87     |
| Gansmo (2016)    | 1.14 (0.99, 1.32) | 6.69     |
| Gansmo (2016)    | 1.04 (0.90, 1.20) | 6.69     |
| Khanlou (2017)   | 1.02 (0.62, 1.69) | 2.85     |
| Hashemi (2018)   | 0.96 (0.65, 1.42) | 3.82     |
| Pedram (2020)    | 1.27 (0.84, 1.91) | 3.59     |
| DM Zhao (2020)   | 0.76 (0.57, 1.00) | 5.07     |
| Kotarac (2020)   | 0.84 (0.61, 1.14) | 4.65     |
| Overall (1-squared=81.5%, p=0.000) | 0.86 (0.78, 0.96) | 100.00   |

Note: Weights are from random effects analysis
tumor susceptibility and prognosis. The relationship between the MDM4 gene can impact the MDM4 activity and hence malignancy therapy [38]. Single-nucleotide polymorphisms has been investigated extensively as a target spot for target regulate P53 activity and lead to cancer. Meanwhile, MDM4 polymorphisms and various neoplasms was investigated; however, the results were inconsistent. For this reason, it is essential to comprehensively evaluate the relationship between MDM4 polymorphisms and cancers.

Sensitivity Analysis

We conducted a sensitivity analysis of the pooled results to assess the individual impact of each study. Overall findings did not change significantly after sequentially eliminating each included study, showing that the outcomes of this meta-analysis are robust and stable (Supplementary Figures 1-5).

Discussion

As a negative regulator of the P53 protein, MDM4 can down-regulate P53 activity and lead to cancer. Meanwhile, MDM4 has been investigated extensively as a target spot for target-ed malignancy therapy [38]. Single-nucleotide polymorphisms in the MDM4 gene can impact the MDM4 activity and hence tumor susceptibility and prognosis. The relationship between MDM4 polymorphisms and various cancers is essential to comprehensively evaluate the relationship between MDM4 polymorphisms and cancers.

This is the most comprehensive meta-analysis to date to study the association between MDM4 polymorphisms and cancers. We analyzed 5 MDM4 polymorphisms and found that rs4245739 polymorphism was a factor in reducing cancer susceptibility, while the remaining 4 SNPs (rs4245739, rs1563828, rs1180129, rs10900598, and rs1380576) were not associated with malignancies. The findings of meta-analyses by Ming-Jie Wang et al, Chaoyi Xu et al, and Yajing Zhai et al suggest that rs4245739 polymorphism decreases carcinoma susceptibility, and the conclusions were consistent with ours [32-34]; For rs4245739, rs1563828, rs1180129, rs10900598, and rs1380576, Ming-Jie Wang et al and Yajing Zhai et al concluded, in agreement with the present study, that these 4 SNPs were not associated with cancers [32,34]. Xin Jin et al investigated rs4245739 only, and found that this SNP could reduce the risk of cancer in dominant, heterozygous, and additive

| Study ID                   | OR (95% CI) | % weight |
|---------------------------|-------------|----------|
| Garcia-Cionzas (2013)     | 1.16 (1.11, 1.21) | 7.47     |
| JB Liu (2013)             | 0.55 (0.41, 0.75)  | 4.08     |
| JB Liu (2013)             | 0.41 (0.26, 0.66)  | 2.52     |
| LQ Zhou (2013)            | 0.55 (0.37, 0.81)  | 3.19     |
| LQ Zhou (2013)            | 0.67 (0.48, 0.93)  | 3.80     |
| CB Fan (2014)             | 0.46 (0.25, 0.84)  | 1.71     |
| JB Feng (2014)            | 0.92 (0.76, 1.11)  | 5.74     |
| Gansmo (2015)             | 0.92 (0.83, 1.02)  | 6.88     |
| Gansmo (2015)             | 1.02 (0.93, 1.12)  | 7.01     |
| Gansmo (2015)             | 1.03 (0.93, 1.14)  | 6.96     |
| Gansmo (2015)             | 0.95 (0.86, 1.04)  | 6.99     |
| F Gao (2015)              | 0.49 (0.31, 0.78)  | 2.62     |
| F Gao (2015)              | 0.39 (0.23, 0.67)  | 2.10     |
| Pedram (2016)             | 1.21 (0.89, 1.64)  | 4.14     |
| Gansmo (2016)             | 1.07 (0.96, 1.19)  | 6.83     |
| Gansmo (2016)             | 1.01 (0.91, 1.13)  | 6.83     |
| Khanlou (2017)            | 1.00 (0.67, 1.49)  | 3.10     |
| Hashemi (2018)            | 0.90 (0.65, 1.24)  | 3.93     |
| Pedram (2020)             | 1.13 (0.81, 1.56)  | 3.89     |
| DM Zhao (2020)            | 0.73 (0.58, 0.92)  | 5.16     |
| Kotarac (2020)            | 0.83 (0.65, 1.05)  | 5.06     |
| Overall (1-squared=84.6%, p=0.000) | 0.87 (0.79, 0.95)  | 100.00   |

Note: Weights are from random effects analysis.
models, but the opposite was found in the recessive model [35]. Although Yaxuan Wang et al worked on all 5 MDM4 polymorphisms, they only evaluated 3 gene models, including alleles, dominant, and recessive; they found that rs4245739 reduced cancer risk, while the remaining 4 SNP were not associated with cancer [36]. Our meta-analysis was updated with 7 articles, including 48 case-control studies, compared to a similar meta-analysis published recently [36].

Polymorphism rs4245739 (A>C) is the most studied MDM4 gene polymorphism. Thus far, 60 case-control studies were performed to evaluate its relationship with cancer. The most studies (46) have been done on breast cancer [12,14,15,18,20,21]. Two studies from China showed the rs4245739 polymorphism can reduce ESCC risk in the Chinese population [30]. A Chinese study suggested that the rs4245739 polymorphism might be a risk factor for gastric cancer [16]. Studies on colorectal cancer and the SNP reached different conclusions; Zhao et al found that the SNP reduced the risk of colorectal cancer [29], and Gansmo et al concluded that there was no association between these [12]. Gao et al discovered that the rs4245739 polymorphism decreased lung cancer incidence [13], while Gansmo et al concluded that it was not associated with lung cancer [12]. Kotarac et al and Gansmo et al both discovered that this SNP was not associated with prostate cancer [12,17]. Ovarian cancer, endometrial cancer, thyroid cancer, and non-Hodgkin lymphoma have been less studied [10,11,19]. The rs4245739 polymorphism has been reported to be unrelated to endometrial cancer and thyroid cancer, and was reported to be associated with (ER)-negative but not ER-positive breast cancer in their GWAS studies (including 40 case-control studies) [14]. Two studies from China showed the rs4245739 polymorphism can reduce ESCC risk in the Chinese population [30]. A Chinese study suggested that the rs4245739 polymorphism might be a risk factor for gastric cancer [16]. Studies on colorectal cancer and the SNP reached different conclusions; Zhao et al found that the SNP reduced the risk of colorectal cancer [29], and Gansmo et al concluded that there was no association between these [12]. Gao et al discovered that the rs4245739 polymorphism decreased lung cancer incidence [13], while Gansmo et al concluded that it was not associated with lung cancer [12]. Kotarac et al and Gansmo et al both discovered that this SNP was not associated with prostate cancer [12,17]. Ovarian cancer, endometrial cancer, thyroid cancer, and non-Hodgkin lymphoma have been less studied [10,11,19]. The rs4245739 polymorphism has been reported to be unrelated to endometrial cancer and thyroid cancer, and was reported to be associated with

Figure 3. (A) Contour-enhanced funnel plot on the dominant model (CC+AC vs AA) of the relationship between rs4245739 and cancer susceptibility. (B) Contour-enhanced funnel plot on the heterozygous model (AC vs AA) of the relationship between rs4245739 and cancer susceptibility. (C) Contour-enhanced funnel plot on the additive model (C vs A) of the relationship between rs4245739 and cancer susceptibility. (Figures were created using Stata.16.0 and processed with Photoshop. Stata, 16.0, StataCorp. Photoshop, CS6, Adobe Systems Software Ireland, Ltd.)
ovarian cancer and non-Hodgkin lymphoma. Our findings suggest that the rs4245739 polymorphism can reduce cancer risk, especially in subgroups of the Asian populations. In addition, only the risk of ESCC was associated with rs4245739 polymorphism in the subset of cancer types. All 3 teams in the subgroup of the source of controls showed statistical significance, and the mixed group contained only 1 study that showed the opposite result. We investigated the reasons for heterogeneity with meta-regression and subgroup analysis. Through meta-regression, we discovered that heterogeneity originated from ethnicity, and we further discovered that heterogeneity existed mainly in studies on Asian populations, which may also be related to factors such as living environment and diet. The asymmetry of contour-enhanced funnel plots for the dominant, recessive, and additive models may be associated with heterogeneity. However, the results of the Begg’s and Egger’s tests indicated publication bias for all 5 models, so we further evaluated them by the trim and fill method and found the publication bias to be within acceptable limits.

Relatively few studies were conducted for rs1380576 (C>G), rs11801299 (G>A), rs10900598 (G>T) and rs1563828 (C>T) [9,22-28]. Our meta-analysis demonstrated that these 4 SNPs were not associated with tumor sensitivity. However, in ethnic subgroups, we found that the rs1380576 polymorphism could reduce the risk of tumors in Asian populations; therefore, future studies on the rs1380576 polymorphism could regard this as a breakthrough. The analysis of rs11801299, rs10900598, and rs1380576 polymorphisms had a high level of heterogeneity; we speculate that this might be related to variations in tumor type and ethnicity of the included individuals.

MDM2/MDM4 is an endogenous negative regulatory factor of p53, and its expression can be activated by p53, forming a p53-MDM2/MDM4 negative feedback loop [39]. Almost all malignancies present abnormalities in the p53-MDM2/MDM4 loop, mainly involving p53 mutations or MDM2/MDM4 overexpression [40]; this abnormal pathway leads to loss of p53 tumor suppressor activity. Due to its prevalence in a variety of tumors, p53 has long been a potential target for tumor therapy. However, because of its complex mechanism, only a few drugs have entered preliminary clinical trials until recent years, in particular, drugs targeting the MDM2/MDM4 family [41-44]. Therefore, future studies need to define the specific mechanisms by which the p53-MDM2/MDM4 loop plays a role in cancers, as well as feasible interventions. In addition, the screening of populations suitable for p53-related therapy and the search for biomarkers with the predictive value of efficacy will be the focus of future research.

Our study has some potential limitations. First, this meta-analysis suffers from publication bias and heterogeneity. Second, the remaining 4 SNP datasets (rs1563828, rs11801299, rs10900598, and rs1380576) were small, making it difficult to draw reliable conclusions. Third, selective bias exists as only studies from Asian populations versus White populations were included. Fourth, the literature search only included English and Chinese articles.

Conclusions

In conclusion, we demonstrated that the rs4245739 polymorphism reduces the risk of cancers, especially in Asian populations, and it is a risk-reducing factor for ESCC incidence. More studies are needed to further explore the relationship between MDM4 polymorphisms and cancer susceptibility in the future.

Data Availability Statement

The data utilized in this meta-analysis are freely available in the database mentioned in this paper.

This manuscript was created and modified based on the PRISMA 2020 checklist [45].

Acknowledgment

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Declaration of Figures’ Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.
## Supplementary Table 1. Assessment of the quality of the included studies by the Newcastle-Ottawa Scale (NOS).

| Author         | Year | Cancer-type | Selection Criteria | Comparability Criteria | Exposure Criteria | Score |
|----------------|------|-------------|--------------------|------------------------|-------------------|-------|
| rs4245739      |      | Breast cancer | ⭐ ⭐ – ⭐ ⭐ ⭐ – – ⭐ | – ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 5     |
| Garcia-Closas  | 2013 | Breast cancer | ⭐ ⭐ – ⭐ ⭐ ⭐ – – ⭐ | – ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 7     |
| JB Liu         | 2013 | Breast cancer | ⭐ ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 7     |
| LQ Zhou        | 2013 | ESCC         | ⭐ ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 7     |
| CB Fan         | 2014 | NHL          | ⭐ ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 7     |
| JB Feng        | 2014 | Gastric cancer | ⭐ ⭐ – ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 6     |
| Gansmo         | 2015 | Breast cancer | ⭐ ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 7     |
| Gansmo         | 2015 | Colon cancer  | ⭐ ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 7     |
| Gansmo         | 2015 | Lung cancer   | ⭐ ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 7     |
| Gansmo         | 2015 | Prostate cancer | ⭐ ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 7     |
| F Gao          | 2015 | Lung cancer   | ⭐ ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 7     |
| Pedram         | 2016 | Breast cancer | ⭐ ⭐ – ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 6     |
| Gansmo         | 2016 | Ovarian cancer | ⭐ ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 6     |
| Gansmo         | 2016 | Endometrial cancer | ⭐ ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 6     |
| Khanlou        | 2017 | Thyroid cancer | ⭐ ⭐ – ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 6     |
| Hashemi        | 2018 | Breast cancer | ⭐ ⭐ – ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 6     |
| Pedram         | 2020 | Breast cancer | ⭐ ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 6     |
| DM Zhao        | 2020 | Colorectal cancer | ⭐ ⭐ – ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 7     |
| Kotarac        | 2020 | Prostate cancer | ⭐ ⭐ – ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 6     |
| Tripon         | 2020 | AML          | ⭐ ⭐ – ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 6     |
| rs1563828      |      |              | ⭐ ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 6     |
| CG Song        | 2012 | Breast cancer | ⭐ ⭐ – ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 6     |
| YW Zhang       | 2012 | NPC          | ⭐ ⭐ – ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 7     |
| Thunell        | 2014 | Hereditary melanoma | ⭐ ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | ⭐ ⭐ ⭐ ⭐ ⭐ – – ⭐ | 7     |
Supplementary Table 1 continued. Assessment of the quality of the included studies by the Newcastle-Ottawa Scale (NOS).

| Author       | Year | Cancer-type | Selection Criteria 1 | Selection Criteria 2 | Selection Criteria 3 | Selection Criteria 4 | Comparability Criteria 5 | Comparability Criteria 6 | Comparability Criteria 7 | Comparability Criteria 8 | Exposure Criteria 6 | Exposure Criteria 7 | Exposure Criteria 8 | Score |
|--------------|------|-------------|----------------------|----------------------|----------------------|----------------------|--------------------------|--------------------------|--------------------------|--------------------------|---------------------|---------------------|---------------------|-------|
| rs1380576    |      |             | *                    | *                    | –                    | *                    | *                        | *                        | *                        | –                        | –                   | –                   | –                   | 7     |
| HP Yu        | 2011 | SCCHN       | *                    | *                    | –                    | *                    | *                        | *                        | *                        | –                        | –                   | –                   | –                   | 7     |
| HP Yu        | 2012 | SCCHN       | *                    | *                    | –                    | *                    | *                        | *                        | *                        | –                        | –                   | –                   | –                   | 7     |
| GC Wu        | 2015 | Gastric cancer | *                    | *                    | –                    | *                    | *                        | *                        | –                        | –                        | –                   | –                   | –                   | 6     |
| MY Wang      | 2017 | Gastric cancer | *                    | *                    | –                    | *                    | *                        | *                        | –                        | –                        | –                   | –                   | –                   | 6     |
| Hashemi      | 2018 | Breast cancer | *                    | *                    | –                    | *                    | *                        | –                        | –                        | –                        | –                   | –                   | –                   | 6     |
| FH Yu        | 2019 | Retino-blastoma | *                    | *                    | –                    | *                    | *                        | –                        | –                        | –                        | –                   | –                   | –                   | 6     |
| rs11801299   |      |             | *                    | *                    | –                    | *                    | *                        | *                        | *                        | –                        | –                   | –                   | –                   | 7     |
| HP Yu        | 2011 | SCCHN       | *                    | *                    | –                    | *                    | *                        | *                        | *                        | –                        | –                   | –                   | –                   | 7     |
| HP Yu        | 2012 | SCCHN       | *                    | *                    | –                    | *                    | *                        | *                        | *                        | –                        | –                   | –                   | –                   | 7     |
| MY Wang      | 2017 | Gastric cancer | *                    | *                    | –                    | *                    | *                        | –                        | –                        | –                        | –                   | –                   | –                   | 6     |
| Hashemi      | 2018 | Breast cancer | *                    | *                    | –                    | *                    | *                        | –                        | –                        | –                        | –                   | –                   | –                   | 6     |
| FH Yu        | 2019 | Retino-blastoma | *                    | *                    | –                    | *                    | *                        | –                        | –                        | –                        | –                   | –                   | –                   | 6     |
| rs10900598   |      |             | *                    | *                    | –                    | *                    | *                        | *                        | *                        | –                        | –                   | –                   | –                   | 7     |
| HP Yu        | 2011 | SCCHN       | *                    | *                    | –                    | *                    | *                        | *                        | *                        | –                        | –                   | –                   | –                   | 7     |
| HP Yu        | 2012 | SCCHN       | *                    | *                    | –                    | *                    | *                        | *                        | *                        | –                        | –                   | –                   | –                   | 7     |
| MY Wang      | 2017 | Gastric cancer | *                    | *                    | –                    | *                    | *                        | –                        | –                        | –                        | –                   | –                   | –                   | 6     |

Criteria 1 – adequate definition of case; Criteria 2 – representativeness of the case; Criteria 3 – selection of controls; Criteria 4 – definition of controls; Criteria 5 – control for important factor; Criteria 6 – assessment of exposure; Criteria 7 – same method of ascertainment for cases and controls; Criteria 8 – non-response rate.

Supplementary Table 2. Results for meta-regression of rs4245739.

| Covariates         | Number of dummy variables | Dominant model | Recessive model | Heterozygous model | Homozygous model | Additive model |
|--------------------|---------------------------|----------------|----------------|-------------------|-----------------|---------------|
| rs4245739          |                           |                |                |                   |                 |               |
| Publication year   | –                         | 0.580          | 0.363          | 0.653             | 0.361           | 0.486         |
| Ethnicity          | 2                         | <0.001         | 0.548          | <0.001            | 0.534           | <0.001        |
| Cancer type        | 6                         | 0.292          | 0.258          | 0.211             | 0.445           | 0.493         |
| Genotyping methods | 4                         | 0.517          | 0.679          | 0.487             | 0.744           | 0.496         |
| Source of controls | 3                         | 0.275          | 0.412          | 0.203             | 0.358           | 0.291         |
Supplementary Figure 1. Sensitivity analysis of MDM4 rs4245739 and cancer risk in dominant model. (The figure was created using Stata 16.0 and processed with Photoshop. Stata, 16.0, StataCorp. Photoshop, CS6, Adobe Systems Software Ireland, Ltd.)

Supplementary Figure 2. Sensitivity analysis of MDM4 rs4245739 and cancer risk in the recessive model. (The figure was created using Stata 16.0 and processed with Photoshop. Stata, 16.0, StataCorp. Photoshop, CS6, Adobe Systems Software Ireland Ltd.)
Supplementary Figure 3. Sensitivity analysis of MDM4 rs4245739 and cancer risk in heterozygous model. (The figure was created using Stata 16.0 and processed with Photoshop. Stata, 16.0, StataCorp. Photoshop, CS6, Adobe Systems Software Ireland, Ltd.)

Supplementary Figure 4. Sensitivity analysis of MDM4 rs4245739 and cancer risk in homozygous model. (The figure is made by Stata 16.0 and processed by Photoshop. Stata, 16.0, StataCorp. Photoshop, CS6, Adobe Systems Software Ireland, Ltd.)
### Supplementary Figure 5. Sensitivity analysis of MDM4 rs4245739 and cancer risk in the additive model. (The figure was created using Stata 16.0 and processed using Photoshop. Stata, 16.0, StataCorp. Photoshop, CS6, Adobe Systems Software Ireland, Ltd.)

| Study            | Lower CI limit | Estimate | Upper CI limit |
|------------------|----------------|----------|----------------|
| Garcia-Closas (2013) |                |          |                |
| JB Liu (2013)     |                |          |                |
| JB Liu (2013)     |                |          |                |
| LO Zhou (2013)    |                |          |                |
| LO Zhou (2013)    |                |          |                |
| CB Fan (2014)     |                |          |                |
| JB Feng (2014)    |                |          |                |
| Gansmo (2015)     |                |          |                |
| Gansmo (2015)     |                |          |                |
| Gansmo (2015)     |                |          |                |
| Gansmo (2015)     |                |          |                |
| F Gao (2015)      |                |          |                |
| F Gao (2015)      |                |          |                |
| Pedram (2016)     |                |          |                |
| Gansmo (2016)     |                |          |                |
| Gansmo (2016)     |                |          |                |
| Khanlou (2017)    |                |          |                |
| Hashemi (2018)    |                |          |                |
| Pedram (2020)     |                |          |                |
| DM Zhao (2020)    |                |          |                |
| Kotarac (2020)    |                |          |                |

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