Original Article

The prognostic value of homeobox A9 (HOXA9) methylation in solid tumors: a systematic review and meta-analysis

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Background: The prognosis of homeobox A9 (HOXA9) methylation have been assessed in a variety of cancers; nevertheless, the results remain undetermined due to discrete outcome and the limitations of small sample size. Therefore, we conducted a meta-analysis to explore the effect of HOXA9 methylation on the prognostic outcomes of patients with solid tumors.

Methods: Qualified studies were verified by searching PubMed, Excerpta Medica Database and Web of Science until September, 2020. Clinicopathological factors and hazard ratio (HR) of 95% confidence interval (95% CI) were selected. Subgroup analysis including carcinoma category, analysis method and sample size were adopted.

Results: In the meta-analysis 1,031 patients with solid carcinoma from 7 eligible investigations were involved. Among human cancer we discovered that the high HOXA9 methylation level was negative correlative with overall survival (OS) (HR =2.36; 95% CI: 1.70–3.26). In the subgroup analysis, we found HOXA9 methylation over-expression had statistical significance with poorer OS in lung cancer patients (HR =3.08, 95% CI: 1.70–5.55, P=0.002) and non-lung cancer (HR =2.10, 95% CI: 1.42–3.10, P=0.0002). Similar result was found in sample size. Greater than or equal to 100 (HR =2.31, 95% CI: 1.54–3.45, P<0.0001) and less than 100 (HR =2.45, 95% CI: 1.42–4.23, P=0.001).

Discussion: HOXA9 methylation has a significantly estimable biomarker of predicting poor prognosis and a potential target for therapy in solid malignant carcinoma from our meta-analysis.

Keywords: Homeobox A9 methylation (HOXA9 methylation); biomarker; prognosis; solid tumors; meta-analysis

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Introduction

Cancer is primary cause of death worldwide is cancer which remains a global and increasing problem (1). In 2019, 1,762,450 new cancer cases and 606,880 cancer deaths are expected to occur in the United States (2). The main reason for the high mortality rate of cancer is the lack of accurate early diagnosis and effective methods of disease prognostic surveillance. Therefore, there is an instant need to predict

the prognosis of cancers and confirm novel target of early cancer diagnosis.

Tumorigenesis can be taken into account in a malformed modality of organic tissues, and there are many similarities with normal embryo and tumor development (3,4). DNA methylation-based biomarkers have emerged as promising candidates for early cancer detection, prognosis prediction and real-time follow-up of tumor dynamics. What is more, the homeobox (HOX) genes presumably serves as a guidance molecule that is highly conserved evolutionarily among solid tumors, which play an important role in the regulation of embryonic development (5). Then, the research field of HOX in carcinoma has attracted widespread attention in recent years. The human HOX gene contains 39 genes, which have been proposed to be named HOXA, HOXB, HOXC and HOXD on four different chromosomes, respectively, 7p14, 17q21, 12q13 and 2q31 (6). More and more evidence indicated that, de-regulation of HOX gene expression in an imparity of cancers is closely related to the occurrence and development of tumors (7-9). HOXA9 methylation is the most terminal member of the HOXA gene, located on chromosome 7, which encodes transcription factors that are critical for embryogenesis and are associated with carcinogenesis in multiple different cancer types. The human solid malignances with the prognosis role of HOXA9 methylation is disputed. A large number of researches illustrated that elevated HOXA9 methylation in carcinoma tissue was linked to poor overall survival (OS) of patients with different kinds of solid malignances, for instance, head and neck squamous cell carcinoma (10), breast cancer (11), lung cancer (12,13), bladder cancer (14). What is more, these studies on HOXA9 methylation are limited by small sample size and discrete outcomes.

So far, no meta-analysis was to probe into the prognostic value of HOXA9 methylation of human solid malignances. In addition, we conducted a meta-analysis to probe the HOXA9 methylation expression which is linked to clinicopathological elements and OS of carcinoma patients to determine the predictive value of HOXA9 methylation in solid cancer.

We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/tcr-21-765).

Methods

Literature search

A comprehensive literature study was performed on their own by two investigating officers in Web of Science, PubMed and Excerpta Medica Database with deadline of Sep. 1, 2020. The following MeSH terms were utilized in the search strategy design pattern: ("HOXA9 methylation" OR "homeobox A9") AND ("neoplasm" OR "tumor" OR "carcinoma" OR "cancer"). We also manually consulted other relevant articles to determine other qualified studies.

Inclusion and exclusion criteria

Inclusion criteria: (I) the relationship between HOXA9 methylation expression and the prognosis of solid cancers was investigated; (II) the expression level of HOXA9 methylation in tissue samples was identified; (III) hazard ratio (HR) and 95% confidence interval (95% CI) reported or available from provided data; (IV) the link between OS and HOXA9 methylation expression was described; (V) these papers were written in English.

Exclusion criteria: (I) correspondence, reviews, expert opinions and case reports; (II) duplicate publications; (III) studies where data or information was not available.

Study selection and data extraction

We have filtrated the researches via exclusion and inclusion criteria. Two investigating officers independently reviewed and extracted quantitative data from eligible studies. Any dissent is settled by a third investigator. From all eligible studies we can extract the following data using the same standardized information collection form: first author name, country of origin, number of patients, year of publication, category of cancer, test method, follow-up time, HR, and the corresponding 95% CI.

In order to minimize the bias, we preferred to extract HR and 95% CI from multivariate analysis. If not available, 95% CI for Kaplan-Meier curves and HR were recovered using spreadsheet designed and Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/), as previously mentioned.

Assessment of study quality and statistical analysis

The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of all included studies. Studies with NOS scores ≥6 had higher quality. Resolve differences scores through discussion between authors. When $P \leq 0.05$ or $I^2 < 50\%$, the fixed effect model was adopted without considering the heterogeneity. When there was significant inter-study heterogeneity ($P \leq 0.05$ or $I^2 \geq 50\%$), the random effect models

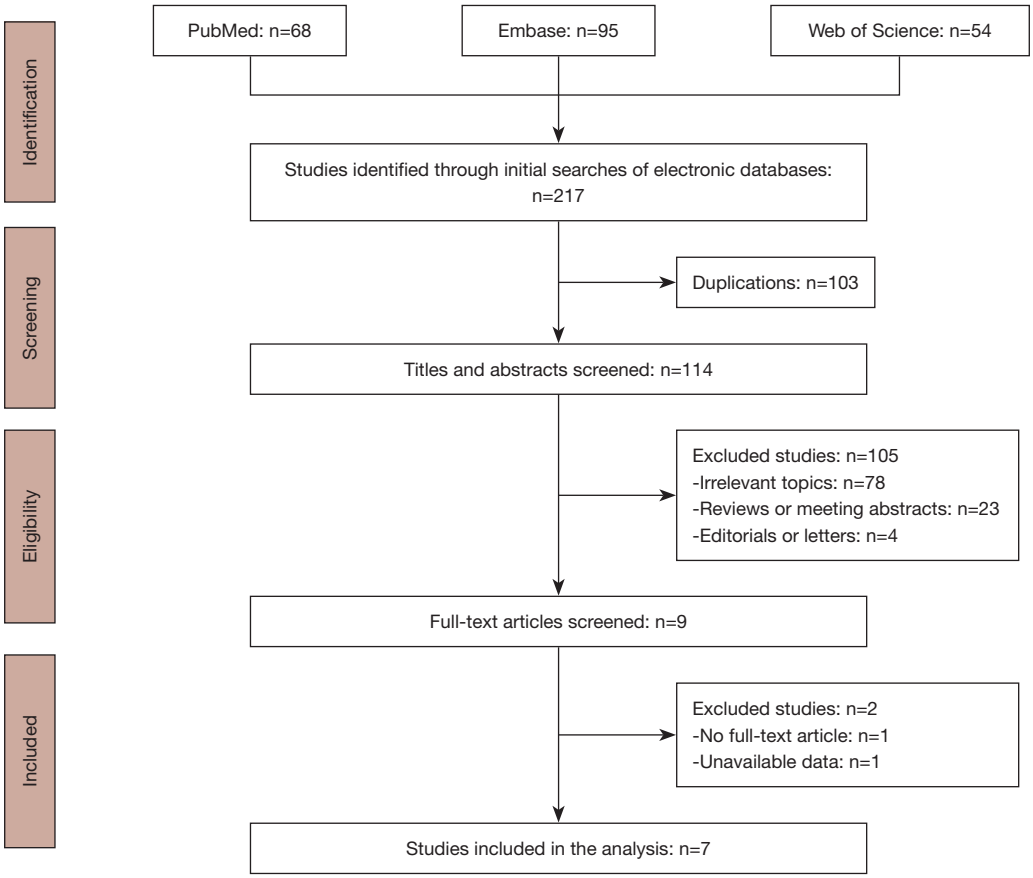

Figure 1 Flow diagram of the literature search and selection.

ware analyzed. The prognostic value of HOXA9 methylation was further analyzed by subgroup analysis. Cochran Q-test and I^2 test were used to evaluate the heterogeneity of combined data. Sensitivity analysis was used to evaluate the stability of the results. To assess potential publication bias, we adopted the Begg's funnel plot and the Egger's test. We applied STATA 12.0 software (STATA Corporation, College Station, TX, USA) to analyze all the data. And P value <0.05 was regarded as statistically significant.

Results

Literature retrieval and analysis

Figure 1 showed the literature retrieval process. First of all, a total of 217 potential investigations were identified using an electronic database search. According to aforementioned exclusion and inclusion criteria, all of seven investigations were finally involved in this analysis. The major features of the enrolled investigations were generalized in *Table 1*. All the enrolled investigations were retrospective, including eight solid carcinomas and published from 2012 to 2015. The final diagnosis of malignancy was determined by histopathological examination.

Relationship between HOXA9 methylation expression and OS

A total of the enrolled investigations suggested the consequences of OS to HOXA9 methylation expression in 1,031 patients. Since there was no inter-study heterogeneity (I^2=0.0%, P_Q=0.932), the fixed effects model was adopted. This meta-analysis of these investigations demonstrated that the high levels of HOXA9 methylation were significantly linked to poorer OS in human cancers (HR =2.36; 95% CI: 1.70–3.26) (*Figure 2*). Patients who have a high HOXA9 methylation expression had worse OS than those who have a low HOXA9 methylation expression.

In addition, the panel meta-analysis was declined,

Table 1 Main characteristic of the eligible studies

Author	Year	Country	Cancer type	Samples	HOXA9 methylation		Cut-off	Detection method	Stage	Analysis method
					High	Low				
Park	2017	Republic of Korea	BCa	82	58	24	NA	IHC	I–IV	Univariate analysis
Sandoval	2013	American	LCa	147	130	17	NA	IHC	I–IV	Kaplan-Meiers
Robles	2015	Japan	LCa	212	68	144	40%	IHC	I–II	Kaplan-Meier
Kim	2013	Republic of Korea	BC	163	81	82	30%	IHC	I–II	Univariate analysis
Hwang	2015	Republic of Korea	LCa	271	191	80	NA	qRT-PCR	NA	Kaplan-Meier
Kitchen	2015	American	BC	48	36	12	25%	qRT-PCR	I–II	Univariate analysis
Zhou	2018	China	HNSCC	108	76	32	30%	IHC	I–III	Univariate analysis

HOXA9 methylation, homeobox A9 methylation; HNSCC, head and neck squamous cell carcinoma; BCa, breast cancer; LCa, lung cancer; BC, bladder cancer; IHC, immunohistochemistry; qRT-PCR, reverse transcription polymerase chain reaction. NA, not available.

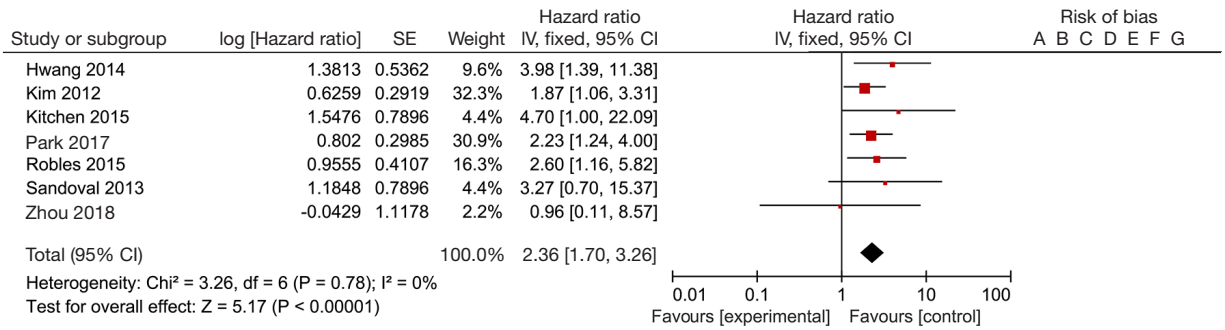

Figure 2 Forest plot for the relationship between HOXA9 methylation expression and OS. HOXA9 methylation, homeobox A9 methylation; OS, overall survival; 95% CI, 95% confidence interval; IV, inverse variance; SE, standard error.

delaminated by sample size, tumor type, nationality and analysis method (*Table 2*). As Stratified analysis was performed according to the type of cancer, HOXA9 methylation over-expression had statistical significance with poorer OS in lung cancer patients (HR =3.08, 95% CI: 1.70–5.55, P=0.002) and non-lung cancer (HR =2.10, 95% CI: 1.42–3.10, P=0.0002). This result was similar obtained by classified analysis of sample size, such as, greater than or equal to 100 (HR =2.31, 95% CI: 1.54–3.45, P<0.0001) and less than 100 (HR =2.45, 95% CI: 1.42–4.23, P=0.001). In addition, HOXA9 methylation over-expression was also found to be linked to poorer OS in researches informed in multivariate analysis (HR =2.10, 95% CI:1.42–3.10, P=0.0002) and non-multivariate analysis (HR =3.08, 95% CI: 1.70–5.55, P=0.002). What is more, in US patients, over-expression of HOXA9 methylation was available related with poor OS (HR =2.24, 95% CI: 1.60–3.15, P<0.00001) or other countries (HR =3.92, 95% CI: 1.31–11.71, P=0.01).

Publication bias

For this meta-analysis of the correlation between HOXA9

Table 2 Results of subgroup analysis of pooled HR of OS of patients with HOXA9 methylation

Stratified analysis	No. of studies	No. of patients	HOXA9 methylation		Pooled HR (95% CI)	P value	Heterogeneity[a]	
			High	Low			I^2 (%)	P value
Cancer type								
Lung cancer	3	630	389	241	3.08 (1.70–5.55)	0.002	0.0	0.82
Non-lung cancer	4	401	251	150	2.10 (1.42–3.10)	0.0002	0.0	0.63
Sample size								
≥100	5	901	546	355	2.31 (1.54–3.45)	<0.0001	0.0	0.65
<100	2	130	94	36	2.45 (1.42–4.23)	0.001	0.0	0.38
Analysis type								
Multivariate	4	401	251	150	2.10 (1.42–3.10)	0.0002	0.0	0.63
Non-multivariate[b]	3	630	389	241	3.08 (1.70–5.55)	0.002	0.0	0.82
Nationality								
American	2	195	166	29	2.24 (1.60–3.15)	<0.00001	0.0	0.69
Non-American	5	836	474	362	3.92 (1.31–11.71)	0.01	0.0	0.75

[a], the fixed-effects model was applied in all subgroup analysis; [b], non-multivariate as the combination of univariate and Kaplan-Meier. HOXA9 methylation, homeobox A9 methylation; HR, hazard ratio; OS, overall survival; 95% CI, 95% confidence interval.

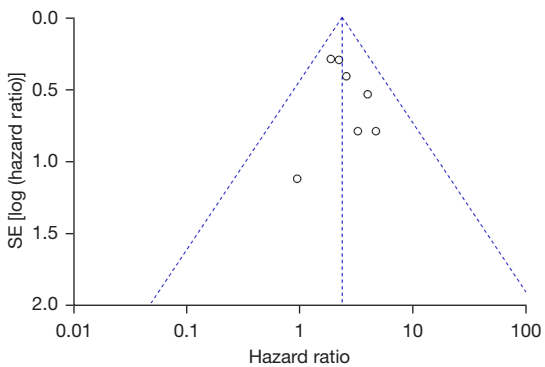

Figure 3 Funnel plot analysis of potential publication bias in the meta-analysis. SE, standard error.

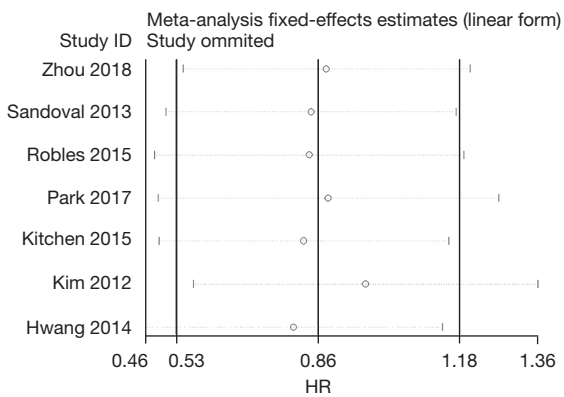

Figure 4 Fixed effects estimates (linear form). HR, hazard ratio.

methylation expression level and overall survival, we used Egger test and Begg funnel plot to evaluate publication bias. As shown in the Begg funnel plot (*Figure 3*), no momentous publication bias was observed in these studies

Sensitivity analysis

Sensitivity analysis could rule out the influence of any individual study on the overall results. Excluding any individual studies, the combined results did not change significantly, indicating robustness of the results (*Figure 4*).

Discussion

A large number of investigations have reported that the HOX gene is of the essence of normal embryogenesis, but is aberrantly expressed in tumors and enrolled in tumor genesis (15). Recently, there has been evidence that methylation of HOX, a member of the HOX gene, participated in progressive disease and tumorigenesis.

Previous research has discovered that compared with corresponding normal or adjacent tissues in different kinds of tumors, HOXA9 methylation value significantly increased in cancer tissues. HOXA9 methylation is catalyzed by a family of HOXA9 methyltransferases (Dnmts) that transfer a methyl group from S-adenyl methionine to the fifth carbon of a cytosine residue to form 5mC. The HOXA9 methylation occurs on cytosines that precede a guanine nucleotide or CpG sites. As a transcription factor, immunohistochemical markers of HOXA9 methylation is predicted localizing in the nucleus of cancer cells, as mentioned previously. However, positive HOXA9 methylation value was fixed in the nucleus and cytoplasm of tumor cells. It is speculated that the reason of cytoplasmic localization perhaps be related to the interaction with cytoplasmic anchoring factors and a regulation of nuclear localization signals supporting nuclear output.

According to the relationship between clinical characteristics and HOXA9 methylation value in human carcinomas, Han *et al.* (16) claimed that higher HOXA9 methylation was associated with advanced Union for International Cancer Control (UICC) stage, histological differentiation, T stage, M stage and recurrence in gastric cancer (GC) patients. Wu *et al.* (17) claimed that the increased HOXA9 methylation value in bladder cancer was linked to advanced stage of TNM, lymphatic invasion and pathological stage. In addition, Kim *et al.* (18) reported that higher HOXA9 methylation may promote the assessment of disease recurrence and progression in NMIBC patients and influence clinical treatment decisions. What is more, Hwang *et al.* (14) claimed which in prostate cancer (PCa) the HOXA9 methylation value was no relationship with histological grade, Gleason score or carcinoma volume, except never-smokers. Furthermore, Gu *et al.* (19) also announced that the HOXA9 methylation value was not statistically significant with its clinical characteristics in head and neck squamous cell carcinoma. For the sake of the prognostic value of HOXA9 methylation in human tumor, several investigations have showed that the higher HOXA9 methylation was affiliated to adverse to the survival of cancerous patients. So, we performed a meta-analysis to evaluate the prognostic value of HOXA9 methylation in cancerous patients. Our meta-analysis offered intensive evidence that patients with higher HOXA9 methylation have poorer OS in tumor patients. What is more, the outcomes of subgroup analyses proposed that an independent prognostic indicator of OS is over-expressed HOXA9 methylation. To sum up, HOXA9 methylation, which might be one of the biomarkers in clinical prediction, may be related to tumor progression to a certain extent.

Several papers have been written in the molecular and cellular mechanisms of HOXA9 methylation on progression and carcinogenesis. Xia *et al.* (20) informed that HOXA9 methylation confirm a carcinogenic effect of miR-652 in uveal melanoma, demonstrating that miR-652 may be a utility biomarker that predict prognosis for patients with uveal melanoma.

Furthermore, PEG10 is up-regulated in hypertrophic cardiomyocytes. PEG10 aggravates cardiac hypertrophy by positively regulating HOXA9 (21). What is more, forced HOXA9 methylation could promote cancer cell migration, proliferation and invasion, while inhibiting tumor cell apoptosis significantly. Yu *et al.* (22) reported that the invasion and invasion mobility could be reduced by this R10-HOXA9 protein, but the proliferation rate could not be reduced, through the non-small cell lung cancer (NSCLC) cells. During *in vitro* and *in vivo*, the developed cell-permeable R10-HOXA9 system could be considered as an effective tool to restrain NSCLC cell migration and invasion. Wang *et al.* (23) reported that CircSMARCA5 inhibited NSCLC cell lines were expressed by Mir-19b-3p/HOXA9 axis. It suggested that circSMARCA5 might provide a target for the remedy of non-small cell lung cancer. Recently, Chen *et al.* (24) claimed that HoxA9 played a significant part in the proliferation and differentiation of leukemia cells *in vitro* and *in vivo*. Nonetheless, the specific and in-depth mechanism still needs further experimental research.

It is known to all that the present research was the first meta-analysis proposing significant proof that higher HOXA9 methylation would be crucially relevant to poorer outcome of patients with solid malignances. Nonetheless, there were still certain limitations to our study. First and foremost, in eligible studies, the critical values for assessing HOXA9 methylation value were inconsistent. Secondly, half of the included studies were conducted in one country, which may limit the applicability of our findings to other races. In addition, in some subgroup analyses, the sample size was comparatively small. What is more, some investigations only provide Kaplan-Meier curves without exact HR and 95% CI, which may lead to inaccurate results. Last but not least, positive results may be more likely to be published than negative consequences, which may lead to the publication bias.

Conclusions

From our analysis, the results illustrate that HOXA9

methylation may play a key part in the progression and aggressiveness of tumor. HOXA9 methylation has a significantly worthwhile biomarker of predicting worse prognosis and a potential therapeutic target in solid malignances from our meta-analysis.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/tcr-21-765

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tcr-21-765). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This article does not contain any studies with human participants or animals performed by any of the authors. All the data involved in this study were extracted from published articles.

References

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7-34.
3. Mahmoudian J, Ghods R, Nazari M, et al. PLAC1: biology and potential application in cancer immunotherapy. Cancer Immunol Immunother 2019;68:1039-58.
4. Gehring WJ, Hiromi Y. Homeotic genes and the homeobox. Annu Rev Genet 1986;20:147-73.
5. Martín-Del-Campo R, Sifuentes-Romero I, García-Gasca A. Hox Genes in Reptile Development, Epigenetic Regulation, and Teratogenesis. Cytogenet Genome Res 2019;157:34-45.
6. Krumlauf R. Hox genes, clusters and collinearity. Int J Dev Biol 2018;62:659-63.
7. Li B, McCrudden CM, Yuen HF, et al. CD133 in brain tumor: the prognostic factor. Oncotarget 2017;8:11144-59.
8. Morgan R, Simpson G, Gray S, et al. HOX transcription factors are potential targets and markers in malignant mesothelioma. BMC Cancer 2016;16:85.
9. Shen LY, Zhou T, Du YB, et al. Targeting HOX/PBX dimer formation as a potential therapeutic option in esophageal squamous cell carcinoma. Cancer Sci 2019;110:1735-45.
10. Zhou C, Ye M, Ni S, et al. DNA methylation biomarkers for head and neck squamous cell carcinoma. Epigenetics 2018;13:398-409.
11. Park SM, Choi EY, Bae M, et al. A long-range interactive DNA methylation marker panel for the promoters of HOXA9 and HOXA10 predicts survival in breast cancer patients. Clin Epigenetics 2017;9:73.
12. Robles AI, Arai E, Mathé EA, et al. An Integrated Prognostic Classifier for Stage I Lung Adenocarcinoma Based on mRNA, microRNA, and DNA Methylation Biomarkers. J Thorac Oncol 2015;10:1037-48.
13. Sandoval J, Mendez-Gonzalez J, Nadal E, et al. A prognostic DNA methylation signature for stage I non-small-cell lung cancer. J Clin Oncol 2013;31:4140-7.
14. Hwang JA, Lee BB, Kim Y, et al. HOXA9 inhibits migration of lung cancer cells and its hypermethylation is associated with recurrence in non-small cell lung cancer. Mol Carcinog 2015;54 Suppl 1:E72-80.
15. Kitchen MO, Bryan RT, Haworth KE, et al. Methylation of HOXA9 and ISL1 Predicts Patient Outcome in High-Grade Non-Invasive Bladder Cancer. PLoS One 2015;10:e0137003.
16. Han Y, Tu WW, Wen YG, et al. Identification and validation that up-expression of HOXA13 is a novel independent prognostic marker of a worse outcome in gastric cancer based on immunohistochemistry. Med Oncol 2013;30:564.
17. Wu Y, Jiang G, Zhang N, et al. HOXA9, PCDH17, POU4F2, and ONECUT2 as a Urinary Biomarker Combination for the Detection of Bladder Cancer in Chinese Patients with Hematuria. Eur Urol Focus

2020;6:284-91.
18. Kim YJ, Yoon HY, Kim JS, et al. HOXA9, ISL1 and ALDH1A3 methylation patterns as prognostic markers for nonmuscle invasive bladder cancer: array-based DNA methylation and expression profiling. Int J Cancer 2013;133:1135-42.
19. Gu ZD, Shen LY, Wang H, et al. HOXA13 promotes cancer cell growth and predicts poor survival of patients with esophageal squamous cell carcinoma. Cancer Res 2009;69:4969-73.
20. Xia Z, Yang C, Yang X, et al. miR-652 Promotes Proliferation and Migration of Uveal Melanoma Cells by Targeting HOXA9. Med Sci Monit 2019;25:8722-32.
21. Wen ZQ, Li SH, Shui X, et al. LncRNA PEG10 aggravates cardiac hypertrophy through regulating HOXA9. Eur Rev Med Pharmacol Sci 2019;23:281-6.
22. Yu SL, Koo H, Lee HY, et al. Recombinant cell-permeable HOXA9 protein inhibits NSCLC cell migration and invasion. Cell Oncol (Dordr) 2019;42:275-85.
23. Wang Y, Li H, Lu H, et al. Circular RNA SMARCA5 inhibits the proliferation, migration, and invasion of non-small cell lung cancer by miR-19b-3p/HOXA9 axis. Onco Targets Ther 2019;12:7055-65.
24. Chen S, Yu J, Lv X, et al. HOXA9 is critical in the proliferation, differentiation, and malignancy of leukaemia cells both in vitro and in vivo. Cell Biochem Funct 2017;35:433-40.

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