ORIGINAL RESEARCH

Association of OPN rs11730582 polymorphism with cancer risk: a meta-analysis

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Purpose: Several molecular epidemiological studies have investigated the association between OPN rs11730582 C>T polymorphism and cancer risk, but the results are inconsistent. Hence, a meta-analysis was conducted to determine the association of this polymorphism with cancer risk.

Materials and methods: The related articles were searched in PubMed, Embase, and Chinese National Knowledge Infrastructure databases. Pooled odds ratios and 95% confidence intervals were calculated to evaluate the strength of the associations. A random-effects model or fixed-effects model was employed depending on the heterogeneity.

Results: A total of ten case-control studies involving 2,749 cancer cases and 3,398 controls were included in the meta-analysis. In overall analysis, OPN rs11730582 C>T polymorphism was not associated with cancer risk. In a stratified analysis by cancer type, no significant association was found between OPN rs11730582 C>T polymorphism and the risk of glioma, gastric cancer, and other cancers.

Conclusion: This meta-analysis suggests that OPN rs11730582 C>T polymorphism is not associated with cancer susceptibility.

Keywords: osteopontin, polymorphism, cancer, risk

Introduction

Cancer has become one of the leading causes of mortality worldwide. Results from GLOBOCAN showed that there were approximately 8.2 million cancer-related deaths in 2012.[1] According to cancer incidence trend, the number of new cancer cases worldwide is expected to reach 22.2 million in 2030.[2] However, the exact mechanism of carcinogenesis remains largely unknown. With the developing of epidemiology, it is becoming clear that genetic variation plays an important role in the development of cancer.[3]

OPN is a secreted, integrin-binding phosphoprotein with chemotactic and cell-adhesive properties both in vitro and in vivo.[4] OPN mainly contributes to host defense, wound healing, and bone formation, by stimulating macrophage migration as well as protecting against viral and bacterial infections through its pro-Th1 effect.[5–7] Furthermore, OPN plays critical roles in various aspects of malignancy, such as invasion and metastasis.[8,9] The human OPN gene has been mapped to chromosome 4q24-q25, and several potential functional polymorphisms in the OPN gene have been identified and noticeably affect its expression.[10] For example, the variant -443 C>T (rs11730582) in the promoter region of OPN gene was found to be located in the transcriptional factor binding site regions, which regulates the transcription of the OPN gene.[10,11] Recently, the associations between OPN rs11730582 polymorphism and cancer risk have been extensively studied. However, previous literature about the

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associations between the OPN rs11730582 polymorphism and risk of cancer has provided inconsistent results.[12–21] For instance, significant associations have been found in nasopharyngeal carcinoma,[13] papillary thyroid cancer,[15] and gastric cancer.[16] However, similar results were not found in intrahepatic cholangiocarcinoma,[10] lung cancer,[17] and gastric cancer.[18] The objective of this meta-analysis is to broadly evaluate the available evidence of the OPN rs11730582 polymorphism and risk of cancer, to derive a more reliable assessment.

Materials and methods

Search strategy

Eligible publications were retrieved by searching PubMed, Embase, and Chinese National Knowledge Infrastructure (CNKI) databases up to August 1, 2015. The search strategy was based on combinations of "osteopontin", "OPN", or "SPP1"; "polymorphism", "variant", or "SNP"; "cancer", "carcinoma", "tumor", or "malignance". Furthermore, we also searched the additional publications from the reference lists of the retrieved articles or reviews which had been previously missed.

Inclusion criteria

All studies selected had to fulfill the following four criteria: 1) case-control study of the OPN rs11730582 C>T polymorphism and cancer risk; 2) the genotype distribution in cases and controls described in detail; 3) genotype distributions of controls consistent with Hardy–Weinberg equilibrium (HWE); 4) when multiple publications reported on the same or overlapping data, only the largest or most recent publication was included.

Data extraction

Data extraction was carried out independently by two reviewers. The following information was extracted from each included publication: the first author's name, year of publication, ethnicity, cancer type, genotyping method, sample size, and numbers of different genotype in all subjects. Discrepancies were adjudicated by discussion.

Statistical analysis

HWE among controls for each study was assessed using Pearson chi-square test and $P_{HWE} \geq 0.05$ was deemed to conform to HWE. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to evaluate the strength of the associations. Five models were conducted: dominant model (CC+CT vs TT), recessive model (CC vs

CT+TT), heterozygote comparison (TC vs TT), homozygote comparison (CC vs TT) and allele model (C vs T). Summary ORs and corresponding 95% CIs were estimated by the fixed-effects model or the random-effects model which was employed depending on the heterogeneity. The heterogeneity among studies was evaluated by a chi-square-based Q test and I^2 statistic. When heterogeneity was absent ($P_h > 0.05$ and $I^2 < 50\%$), a fixed-effects model was applied; otherwise, a random-effects model was employed. Sensitivity analysis was conducted to assess the stability of the combined results by the omission of every single study each time. Finally, the Begg's funnel plot and Egger's test were used to estimate the possible publication bias. $P_E < 0.05$ indicated the presence of potential publication bias. All the analyses were performed using STATA (version 12.0) software (StataCorp LP, College Station, TX, USA).

Results

Characteristics of studies

As shown in Figure 1, a total of 31 records were identified from PubMed, Embase, and CNKI. After reviewing the titles and abstracts of articles, 15 articles were excluded, mainly due to no relevance, being reviews, or functional studies. Sixteen full-text articles that met the crude inclusion criteria were further evaluated for eligibility. Finally, ten eligible studies were included in the meta-analysis. The main characteristics of eligible studies are summarized in Table 1. All selected studies containing 2,749 cases and 3,398 controls were carried out in Asian countries. The studied cancer types included intrahepatic cholangiocarcinoma, nasopharyngeal carcinoma, glioma, papillary thyroid cancer, gastric cancer, lung cancer, cervical cancer, and oral carcinogenesis. In addition, genotype distributions in the controls of all selected studies are in agreement with HWE.
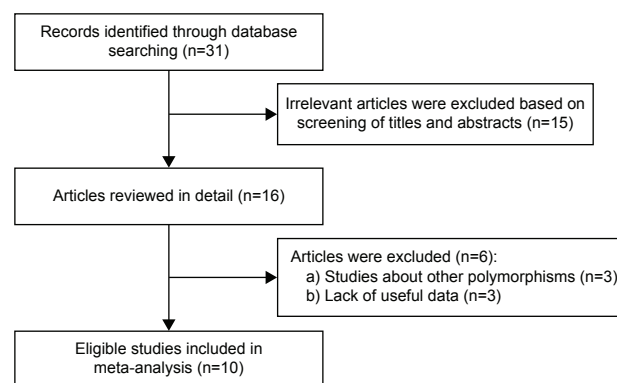
Figure 1 Flow chart of study selection in the meta-analysis.

Table 1 Characteristics of the studies included in the meta-analysis

Author	Year	Ethnicity	Cancer type	Genotyping	Number of cases/controls	Genotypes distribution (TT/CT/CC)		P_{HWE}
						Case	Control	
Zhao et al[12]	2014	Asian	Intrahepatic cholangiocarcinoma	Sequencing	260/260	120/111/29	114/115/31	0.81
Wang et al[13]	2014	Asian	Nasopharyngeal carcinoma	PCR-RFLP	108/210	60/38/10	85/95/30	0.68
Shen et al[14]	2014	Asian	Glioma	TaqMan	248/281	54/113/81	90/137/54	0.88
Mu et al[15]	2013	Asian	Papillary thyroid cancer	TaqMan	363/413	73/171/119	164/187/62	0.47
Lee et al[16]	2013	Asian	Gastric cancer	Pyrosequencing	146/128	59/66/21	65/55/8	0.42
Chen et al[17]	2013	Asian	Lung cancer	Sequencing	360/360	164/165/31	153/163/44	0.95
Zhao et al[18]	2012	Asian	Gastric cancer	Sequencing	200/200	91/94/15	85/93/22	0.65
Xu et al[19]	2011	Asian	Cervical cancer	TaqMan	300/774	227/49/24	334/334/106	0.13
Chiu et al[20]	2010	Asian	Oral carcinogenesis	Sequencing	97/100	47/41/9	33/50/17	0.79
Chen et al[21]	2010	Asian	Glioma	PCR-LDR	670/680	299/299/69	284/311/77	0.56

Abbreviations: PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-LDR, polymerase chain reaction-ligation detection reaction; HWE, Hardy-Weinberg equilibrium.
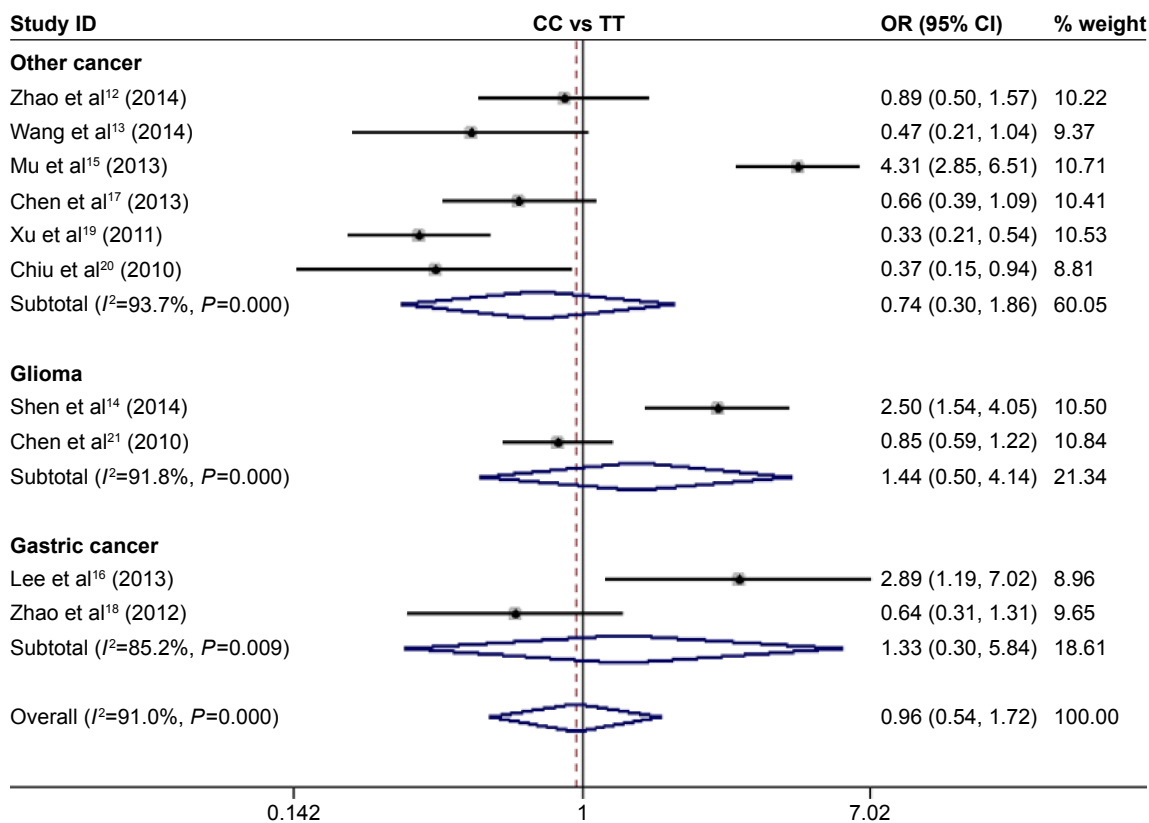
Quantitative synthesis

The pooled results of meta-analysis for the association between OPN rs11730582 polymorphism and cancer risk are shown in Table 2 and Figure 2. In overall analysis, OPN rs11730582 C>T polymorphism was not associated with cancer risk (CC vs TT: OR, 0.96; 95% CI, 0.54–1.72; CT vs TT: OR, 0.85; 95% CI, 0.58–1.26; CC+CT vs TT: OR, 0.89; 95% CI, 0.58–1.37; CC vs CT+TT: OR, 1.00; 95% CI, 0.66–1.53; C vs T: OR, 0.93; 95% CI, 0.66–1.30). In a stratified analysis by cancer type, no significant association was found between OPN rs11730582 C>T polymorphism and the risk of glioma (CC vs TT: OR, 1.44; 95% CI, 0.50–4.14; CT vs TT: OR, 1.08; 95% CI, 0.73–1.60; CC+CT vs TT: OR, 1.21; 95% CI, 0.65–2.24; CC vs CT+TT: OR, 1.34;

Table 2 Meta-analysis of the association of OPN rs11730582 polymorphism with cancer risk

Study groups	Test of heterogeneity			Test of association		
	I^2, %	P_h	Model	OR (95% CI)	Z	P_z
Overall						
CC vs TT	91.0%	<0.01	R	0.96 (0.54–1.72)	0.14	0.89
CT vs TT	91.0%	<0.01	R	0.85 (0.58–1.26)	0.80	0.43
CC+CT vs TT	93.4%	<0.01	R	0.89 (0.58–1.37)	0.53	0.59
CC vs CT+TT	85.4%	<0.01	R	1.00 (0.66–1.53)	0.02	0.98
C vs T	94.4%	<0.01	R	0.93 (0.66–1.30)	0.44	0.66
Glioma						
CC vs TT	91.8%	<0.01	R	1.44 (0.50–4.14)	0.68	0.50
CT vs TT	64.6%	0.09	R	1.08 (0.73–1.60)	0.37	0.71
CC+CT vs TT	86.9%	0.01	R	1.21 (0.65–2.24)	0.60	0.55
CC vs CT+TT	89.5%	<0.01	R	1.34 (0.60–3.01)	0.71	0.48
C vs T	92.9%	<0.01	R	1.21 (0.70–2.09)	0.68	0.50
Gastric cancer						
CC vs TT	85.2%	0.01	R	1.33 (0.30–5.84)	0.37	0.71
CT vs TT	3.1%	0.31	F	1.08 (0.79–1.49)	0.48	0.63
CC+CT vs TT	65.8%	0.09	R	1.14 (0.67–1.94)	0.49	0.63
CC vs CT+TT	82.8%	0.02	R	1.25 (0.34–4.69)	0.34	0.74
C vs T	82.6%	0.02	R	1.14 (0.65–1.99)	0.45	0.65
Other cancer						
CC vs TT	93.7%	<0.01	R	0.74 (0.30–1.86)	0.63	0.53
CT vs TT	94.4%	<0.01	R	0.71 (0.36–1.39)	1.00	0.32
CC+CT vs TT	95.7%	<0.01	R	0.73 (0.36–1.49)	0.87	0.39
CC vs CT+TT	89.0%	<0.01	R	0.84 (0.44–1.61)	0.53	0.60
C vs T	96.3%	<0.01	R	0.79 (0.45–1.38)	0.84	0.40

Abbreviations: P_h, P-value of heterogeneity test; P_z, P-value of Z test; R, random-effects model; F, fixed-effects model; OR, odds ratio; CI, confidence interval.

Study ID	CC vs TT	OR (95% CI)	% weight

Other cancer
Zhao et al[12] (2014) — 0.89 (0.50, 1.57) 10.22
Wang et al[13] (2014) — 0.47 (0.21, 1.04) 9.37
Mu et al[15] (2013) — 4.31 (2.85, 6.51) 10.71
Chen et al[17] (2013) — 0.66 (0.39, 1.09) 10.41
Xu et al[19] (2011) — 0.33 (0.21, 0.54) 10.53
Chiu et al[20] (2010) — 0.37 (0.15, 0.94) 8.81
Subtotal (I^2=93.7%, P=0.000) — 0.74 (0.30, 1.86) 60.05

Glioma
Shen et al[14] (2014) — 2.50 (1.54, 4.05) 10.50
Chen et al[21] (2010) — 0.85 (0.59, 1.22) 10.84
Subtotal (I^2=91.8%, P=0.000) — 1.44 (0.50, 4.14) 21.34

Gastric cancer
Lee et al[16] (2013) — 2.89 (1.19, 7.02) 8.96
Zhao et al[18] (2012) — 0.64 (0.31, 1.31) 9.65
Subtotal (I^2=85.2%, P=0.009) — 1.33 (0.30, 5.84) 18.61

Overall (I^2=91.0%, P=0.000) — 0.96 (0.54, 1.72) 100.00

0.142   1   7.02

Figure 2 Meta-analysis of the association between rs11730582 polymorphism and cancer risk under CC vs TT.
Note: Weights are from random-effects analysis.
Abbreviations: OR, odds ratio; CI, confidence interval.

95% CI, 0.60–3.01; C vs T: OR, 1.21; 95% CI, 0.70–2.09), gastric cancer (CC vs TT: OR, 1.33; 95% CI, 0.30–5.84; CT vs TT: OR, 1.08; 95% CI, 0.79–1.49; CC+CT vs TT: OR, 1.14; 95% CI, 0.67–1.94; CC vs CT+TT: OR, 1.25; 95% CI, 0.34–4.69; C vs T: OR, 1.14; 95% CI, 0.65–1.99) and other cancer (CC vs TT: OR, 0.74; 95% CI, 0.30–1.86; CT vs TT: OR, 0.71; 95% CI, 0.36–1.39; CC+CT vs TT: OR, 0.73; 95% CI, 0.36–1.49; CC vs CT+TT: OR, 0.84; 95% CI, 0.44–1.61; C vs T: OR, 0.79; 95% CI, 0.45–1.38).

Sensitivity analysis and publication bias

A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set on the pooled ORs. As shown in Figure 3, no single study influenced the overall results qualitatively, which indicates that our results were statistically robust. Begg's funnel plot and Egger's test were performed to assess the publication bias of literature. As shown in Figure 4, the shapes of the funnel plots did not reveal any evidence of obvious asymmetry. The statistical results of Egger's test still did not show publication bias (P_E=0.51 for CC vs TT, P_E=0.91 for CT vs TT, P_E=0.83 for CC+CT vs TT, P_E=0.25 for CC vs CT+TT, P_E=0.63 for C vs T).

Discussion

Previous studies have reported an inconsistent association between OPN rs11730582 polymorphism and cancer risk. Although the inconsistent results of OPN rs11730582 polymorphism and cancer risk cannot be clarified, it might be due to studies with inadequate statistical power, and different cancer types; and because a single study might be underpowered to explain the role of OPN rs11730582 polymorphism in cancer risk. Furthermore, a meta-analysis is a very powerful tool for analyzing cumulative data of studies where the individual sample sizes are small and the statistical power low. Thus, we performed this meta-analysis attempting to acquire a more accurate result. To the best of our knowledge, this is the largest and most comprehensive meta-analysis for the association of interest. In the current meta-analysis, we included all the studies investigating the association between OPN rs11730582 polymorphism and cancer risk. We did not find any association between OPN rs11730582 polymorphism and cancer risk.

Although our result is suggestive, some limitations of our meta-analysis should be considered in interpreting the results. Firstly, the present conclusion was drawn based
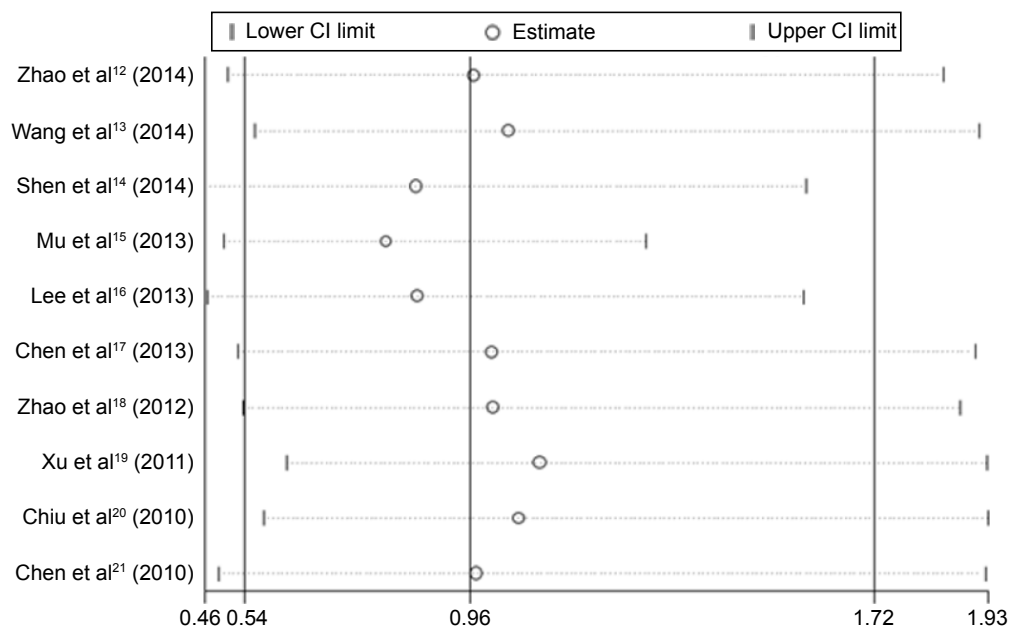
Figure 3 Sensitivity analysis of the association between rs11730582 polymorphism and cancer risk under CC vs TT.
Note: Meta-analysis estimates, given named study is omitted to assess the effect of each study on the pooled ORs.
Abbreviations: CI, confidence interval; OR, odds ratio.

on unadjusted estimates, while a more precise analysis should be conducted by adjusting other covariates including age, lifestyle, and environmental factors. Secondly, the number of cases and controls in the included studies was not enough. Therefore, further large and well-designed studies are required for confirmation. Finally, all studies were from an Asian population, and studies based on other ethnic groups should be performed to re-evaluate the association.

In conclusion, our investigations suggested that the OPN rs11730582 polymorphism might not contribute to the susceptibility of cancer risk.
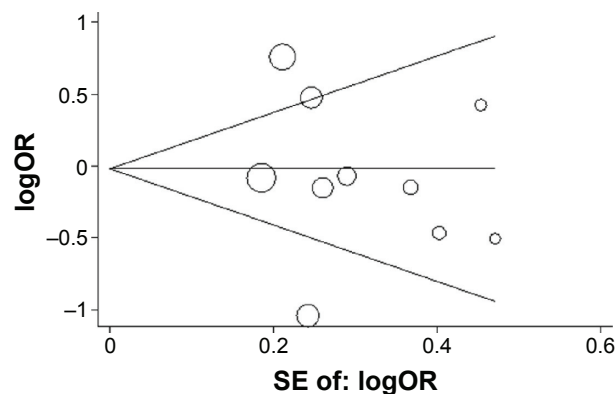
Figure 4 Begg's funnel plot of rs11730582 polymorphism and cancer risk under CC vs TT.
Note: Begg's funnel plot with pseudo 95% confidence limits.
Abbreviations: OR, odds ratio; SE, standard error.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87–108.
2. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. *Lancet Oncol*. 2012;13(8):790–801.
3. Gao X, Wang J, Wang W, Wang M, Zhang J. eNOS Genetic Polymorphisms and Cancer Risk: A Meta-Analysis and a Case-Control Study of Breast Cancer. *Medicine (Baltimore)*. 2015;94(26):e972.
4. Oldberg A, Franzén A, Heinegård D. Cloning and sequence analysis of rat bone sialoprotein (osteopontin) cDNA reveals an Arg-Gly-Asp cell-binding sequence. *Proc Natl Acad Sci U S A*. 1986;83(23):8819–8823.
5. Ashkar S, Weber GF, Panoutsakopoulou V, et al. Eta-1 (osteopontin): an early component of type-1 (cell-mediated) immunity. *Science*. 2000; 287(5454):860–864.
6. Liaw L, Birk DE, Ballas CB, Whitsitt JS, Davidson JM, Hogan BL. Altered wound healing in mice lacking a functional osteopontin gene (spp1). *J Clin Invest*. 1998;101(7):1468–1478.
7. Singh K, DeVouge MW, Mukherjee BB. Physiological properties and differential glycosylation of phosphorylated and nonphosphorylated forms of osteopontin secreted by normal rat kidney cells. *J Biol Chem*. 1990;265(30):18696–18701.
8. Wai PY, Kuo PC. The role of Osteopontin in tumor metastasis. *J Surg Res*. 2004;121(2):228–241.
9. Rittling SR, Chambers AF. Role of osteopontin in tumour progression. *Br J Cancer*. 2004;90(10):1877–1881.
10. Giacopelli F, Marciano R, Pistorio A, et al. Polymorphisms in the osteopontin promoter affect its transcriptional activity. *Physiol Genomics*. 2004;20(1):87–96.
11. Schultz J, Lorenz P, Ibrahim SM, Kundt G, Gross G, Kunz M. The functional -443T/C osteopontin promoter polymorphism influences osteopontin gene expression in melanoma cells via binding of c-Myb transcription factor. *Mol Carcinog*. 2009;48(1):14–23.

12. Zhao XQ, Ma HX, Su MS, He L. Osteopontin promoter polymorphisms at locus – 443 are associated with metastasis and poor prognosis of human intrahepatic cholangiocarcinoma in Chinese population. *Int J Clin Exp Pathol*. 2014;7(10):6914–6921.

13. Wang J, Nong L, Wei Y, Qin S, Zhou Y, Tang Y. Association of osteopontin polymorphisms with nasopharyngeal carcinoma risk. *Hum Immunol*. 2014;75(1):76–80.

14. Shen Z, Chen B, Hou X, Chen P, Zhao G, Fan J. Polymorphism -433 C>T of the Osteopontin gene is associated with the susceptibility to develop gliomas and their prognosis in a Chinese cohort. *Cell Physiol Biochem*. 2014;34(4):1190–1198.

15. Mu G, Wang H, Cai Z, Ji H. OPN -443C>T genetic polymorphism and tumor OPN expression are associated with the risk and clinical features of papillary thyroid cancer in a Chinese cohort. *Cell Physiol Biochem*. 2013;32(1):171–179.

16. Lee TY, Lin JT, Wu CC, et al. Osteopontin promoter polymorphisms are associated with susceptibility to gastric cancer. *J Clin Gastroenterol*. 2013;47(6):e55–e59.

17. Chen Y, Liu H, Wu W, Li Y, Li J. Osteopontin genetic variants are associated with overall survival in advanced non-small-cell lung cancer patients and bone metastasis. *J Exp Clin Cancer Res*. 2013;32:45.

18. Zhao F, Chen X, Meng T, Hao B, Zhang Z, Zhang G. Genetic polymorphisms in the osteopontin promoter increases the risk of distance metastasis and death in Chinese patients with gastric cancer. *BMC Cancer*. 2012;12:477.

19. Xu Q, Yuan B, Xue F, et al. OPN gene polymorphisms are associated with susceptibility and clinicopatholigical characteristics of cervical cancer in a Chinese cohort. *Cancer Biomark*. 2011;10(5):233–239.

20. Chiu YW, Tu HF, Wang IK, et al. The implication of osteopontin (OPN) expression and genetic polymorphisms of OPN promoter in oral carcinogenesis. *Oral Oncol*. 2010;46(4):302–306.

21. Chen J, Wu Q, Lu Y, et al. SPP1 promoter polymorphisms and glioma risk in a Chinese Han population. *J Hum Genet*. 2010;55(7):456–461.