Correlation between non-metastatic protein 23 expression and clinicopathological features of colorectal cancer in Asians

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ABSTRACT. The current meta-analysis was performed to investigate the association between non-metastatic protein 23 (NM23) expression, tumor pathology, and disease prognosis in colorectal cancer (CRC) among Asians. English and Chinese language-based electronic databases (e.g., PubMed, EBSCO, Ovid, Springerlink, Wiley, Web of Science, Wanfang databases, China National Knowledge Infrastructure, VIP databases) were searched using search terms to identify published studies relevant to NM23 and CRC with immunohistochemistry. In total, 289 studies were identified through database searches, and 16 cohort studies (4 studies in English, 12 in Chinese) were chosen for meta-analysis, which included 1592 CRC patients. The results revealed that NM23 protein expression in CRC tissue was higher in patients with Dukes stages A and B than in patients with Dukes stages C and D. The NM23 protein was expressed at higher levels in well- and moderately differentiated tumors than in poorly differentiated tumors. The 5-year survival rate was also higher in CRC patients with NM23-positive tumors than in CRC patients with NM23-negative tumors. Significantly, 5-year tumor relapse and metastasis were lower in patients with NM23-positive tumors than in CRC patients with NM23-negative

tumors. The findings suggest that NM23 expression status is associated with tumor aggressiveness and survival in CRC among Asians. Importantly, CRC patients with NM23-positive tumors had a better prognosis, and thus NM23 expression maybe used as a key prognostic indicator for CRC.

Key words: Colorectal cancer; Meta-analysis; Non-metastatic protein 23; Pathological characteristics; Prognosis

INTRODUCTION

Colorectal cancer (CRC) accounts for approximately 1.25 million newly diagnosed cases each year and is responsible for more than 600,000 cancer-related mortality worldwide (Qu et al., 2013). It is the third leading cause of cancer deaths in the US and the third most common cancer in the US and UK, with over 37,000 new diagnoses in the UK each year (Siegel et al., 2014). The highest rates are observed in developed countries such as Australia, New Zealand, Europe, and the US, while low rates are found in Africa and south-central Asia (Merika et al., 2010). The symptoms and signs of CRC vary depending on the location of the tumor and if metastasis has occurred. General symptoms include rectal bleeding, diarrhea, constipation, loss of weight, abdominal pain, and anemia (Astin et al., 2011; John et al., 2011). CRC staging is conducted based on the TNM system or Dukes staging, which convey the local extent of tumor, lymphatic spread, venous spread, and histologic grading. Typically, for Dukes stage A, the cancer is only present in the inner lining of the bowel; in Dukes stage B, the cancer has invaded the muscle; in Dukes stage C, the cancer has invaded the nearby lymph nodes; in Dukes stage D, the cancer has metastasized (Obrocea et al., 2011; Iinuma et al., 2011). Approximately 75-95% of CRC cases are associated with lifestyle risk factors, aging, and underlying genetic risks (Cunningham et al., 2010; Watson and Collins, 2011). It is thought that the *Ang-2*, *Tie-2*, *PI3K*, and *AKT* genes are correlated with differentiation level, stage of Dukes classification, and lymphatic metastasis in CRC (Zhang et al., 2014). CRCs are aggressive, and 20-50% of CRC patients die within 5 years after diagnosis because of extensive metastatic disease spread (Tan et al., 2012). Furthermore, relapse and metastasis are the leading causes of deaths in CRC, with greater than 50% of CRC patients developing metastases with unresectable tumors (Qu et al., 2013). Therefore, significant efforts have been directed towards early detection and biomarker discovery for CRC (Jimenez et al., 2010).

Non-metastatic gene 23 (*NM23*) (encoded by *NME1*), was discovered because of its reduced expression in a comparative hybridization screen of poorly versus highly metastatic sublines of the murine melanoma cell line K-1735 in 1988 and is the first metastasis suppressor gene discovered fromover 20 metastasis suppressor genes known to date (Marshall et al., 2010). NM23 is thought to have a dual role, as its expression is induced in primary cancers, but its loss of expression at later stages promotes tumor progression (Saha and Robertson, 2011). Multiple biochemical functions have been identified for NM23 proteins, and several may have anti-metastatic properties (Steeg et al., 2011). Cell lines from multiple histological types of cancer were suppressed from undergoing metastasis by NM23. However, no studies have shown that overexpression of NM23 completely abrogated metastasis (Marino et al., 2012). Tumor metastasis is a complex multistep process and involves alterations in multiple genes that influence the spread of tumor cell origin sites to distant metastatic sites in the body. The process is characterized by series of events such as activation/inactivation of metastasis-regulating genes, altered cell adhesion, increased cell

motility, expression of protein hydrolases, and formation of new blood vessels (Tan et al., 2012; Qu et al., 2013). *NM23-H1* was the first identified metastasis suppressor gene and belongs to a group of 8 closely related genes, *Nm23H1-H8*. These *NM23* genes are likely regulated independently because *NM23-H4*, *NM23-H6*, and *NM23-H7* were found to be overexpressed in gastric cancer and CRC (Lu et al., 2013). The exact mechanism for the origin and development of CRC remains unclear. Previous studies have shown that inactivation of NM23 plays an important role in the development of CRC (Wu et al., 2013; Qu et al., 2013). We explored the correlation between NM23 expression, tumor pathology, and tumor prognosis to better understand the influence of NM23 status on CRC progression and survival.

MATERIAL AND METHODS

Literature search

To identify all relevant studies that assessed the correlation between NM23 expression and CRC, we comprehensively searched the PubMed, Web of Science, Cochrane Library, CISCOM, CINAHL, China Bio Medicine, VIP, Wanfang, and China National Knowledge Infrastructure databases (last updated search in September 2014) using search terms related to CRC and NM23. The search terms included the following: ("Colorectal Neoplasms" or "Colonic Neoplasms" or "Rectal Neoplasms" or "Cecal Neoplasms" or "Colorectal Tumor" or "Colonic Tumor" or "Rectal Tumor" or "Cecal Tumor" or "Colorectal Cancer" or "Colonic Cancer" or "Rectal Cancer" or "Cecal Cancer") and ("NM23" or "NM23 Protein"). We further scanned the bibliographies of relevant articles manually to identify additional relevant papers.

Study selection

Selected studies were included in the meta-analysis if they met the following inclusion criteria: 1) clear data were presented and related to an association between NM23 expression, pathological characteristics, and prognosis of CRC; 2) the patients had a confirmed diagnosis of CRC; 3) the studies contained the required statistical data; 4) the language was restricted to Chinese and English. The major exclusion criteria were as follows: 1) insufficient information; 2) duplicate publications; 3) unclear diagnostic criteria for CRC patients.

Data extraction and quality assessment

Data were extracted from the selected studies by 2 independent investigators. Information collected included the following: surname and initials of the first author, year of submission, country, study design, gender, demographic variables, detection method of NM23 expression, and NM23 expression levels, among other points. The 2 investigators assessed the quality of the cohort trials using the Newcastle-Ottawa Scale (NOS) criteria (Stang, 2010). The NOS criteria are as follows: 1) representativeness of the exposed cohort; selection of the non-exposed cohort; ascertainment of exposure; demonstration that the outcome of interest was not present at the start of study; 2) whether the study was selected and analyzed according to the most important factor; whether the study controlled other confounding factors; 3) whether follow-up was long enough for outcomes to occur; adequacy of follow-up of cohorts. Disagreements between the 2 independent investigators were resolved by a third investigator.

Statistical analysis

The meta-analysis was conducted using STATA 12.0 (Stata Corp., College Station, TX, USA). The association between NM23 expression, tumor pathology, and prognosis of CRC was estimated by the standardized mean difference and 95%CI. We used Cochran's *Q*-statistic ($P_h < 0.05$ was considered to be significant) and I^2 tests to quantify heterogeneity among studies (Zintzaras and Ioannidis, 2005b). In order to calculate the pool standardized mean differences, the fixed-/random-effect models were used; the random-effect model was applied when significant heterogeneity was observed ($P_h < 0.05$ or I^2 test exhibited >50%), whereas standardized mean differences were pooled based on the fixed-effect model (Higgins and Thompson, 2002; Zintzaras and Ioannidis, 2005a). In addition, the effect of publication bias was detected by the Egger linear regression test ($P < 0.05$ was considered to be significant), which can be used to evaluate the funnel plot asymmetry, revealing possible publication bias (Song and Gilbody, 1998; Peters et al., 2006).

RESULTS

Demographic variables

Figure 1 shows the flow chart of study selection based on exclusion criteria. First, 289 potential articles were identified from the databases using search terms and manual review. Of the 289 articles, 94 studies were duplicates and were removed. After screening of the title and abstract, 154 studies were found to be irrelevant and subsequently excluded. Of the remaining studies, 20 were excluded after more detailed reading of the full text. Qualitative analysis was performed on 21 studies selected. Finally, 16 studies published from 1999-2014 were incorporated into our meta-analysis (Feng et al., 1999; He et al., 2000; Yu et al., 2000; Liu and Wang, 2001; Wang et al., 2001; Zhen et al., 2002; Zhang et al., 2003; Su and Li, 2004; Liu et al., 2005; Ba, 2006; Gao, 2006; Chen et al., 2007; Song et al., 2010; Wu et al., 2013; Qu et al., 2013; Cui et al., 2014). The baseline characteristics and NOS scores of the 16 eligible studies are summarized in Table 1 and Figure 2, respectively.

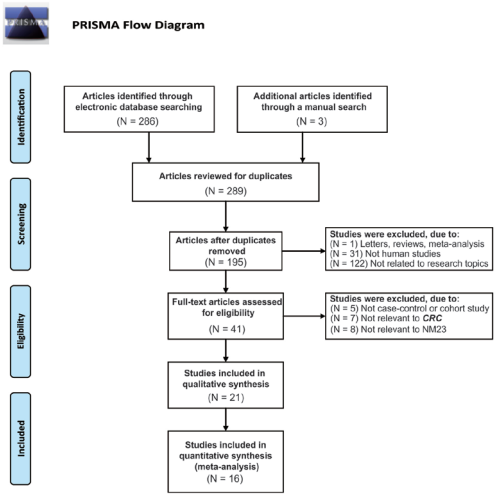


Figure 1. Flow chart shows the study selection procedure. Sixteen studies were included in the meta-analysis.

Table 1. Baseline characteristics for the 16 eligible studies.

First author	Year	Language	Disease	Detecting method	Follow-up duration (months)	Sample size	Gender (M/F)	Age (years)	Study design	Outcome
Feng MH	1999	Chinese	Rectal cancer	IHC	85	82	43/39	48	Cohort	c/d
He JJ	2000	Chinese	CRC	IHC	60	101	62/39	50.6 (24-75)	Cohort	c/e
Yu BP	2000	Chinese	CRC	IHC	**	58	38/20	63 (24-79)	Cohort	a/b
Liu YF	2001	Chinese	Colon cancer + Rectal cancer	IHC	45	280	148/132	59.2 (21-82)	Cohort	c/e
Wang XS	2001	Chinese	Colon cancer	IHC	132	101	54/47	50.6 (20-77)	Cohort	a/b/c/d
Zheng BA	2002	Chinese	CRC	IHC	**	73	45/28	49 (18-86)	Cohort	a/b
Zhang JB	2003	Chinese	CRC	IHC	>120	28	NR	NR	Cohort	c
Su ZH	2004	English	Colon cancer	IHC	**	32	11/22	22-77	Cohort	a/b
Liu J	2005	Chinese	Rectal cancer	IHC	**	82	49/33	58.4 ± 11.5	Cohort	a/b
Ba YP	2006	Chinese	CRC	IHC	>60	121	79/42	58.4 (26-75)	Cohort	a/b/c/e
Gao FL	2006	Chinese	CRC	IHC	>60	85	56/29	53.7 (37-78)	Cohort	a/b/c/d
Chen WC	2007	English	CRC	IHC	**	85	48/37	58 (30-86)	Cohort	a/b
Song F	2010	Chinese	Colon cancer + Rectal cancer	IHC	**	83	56/27	61 (29-90)	Cohort	b
Qu LJ	2013	English	CRC	IHC	**	98	69/29	57.84 (27-79)	Cohort	b
Wu HW	2013	English	CRC	IHC	**	87	56/31	59 (35-82)	Cohort	b
Cui JJ	2014	Chinese	Colon cancer + Rectal cancer	IHC	**	196	72/124	61 (34-81)	Cohort	b

CRC = colorectal cancer; IHC = immunohistochemistry; M = male; F = female; NR = not reported; a, positive expression of NM23 (Dukes classification: A+B *vs* C+D); b, positive expression of NM23 (histological type of adenocarcinoma: high/moderate differentiation *vs* low differentiation); c, 5-year survival rate (NM23+ *vs* NM23-); d, positive expression of NM23 (overall survival (OS) ≥ 5 years *vs* OS < 5 years); e, 5-year recurrence/metastasis (NM23+ *vs* NM23-).

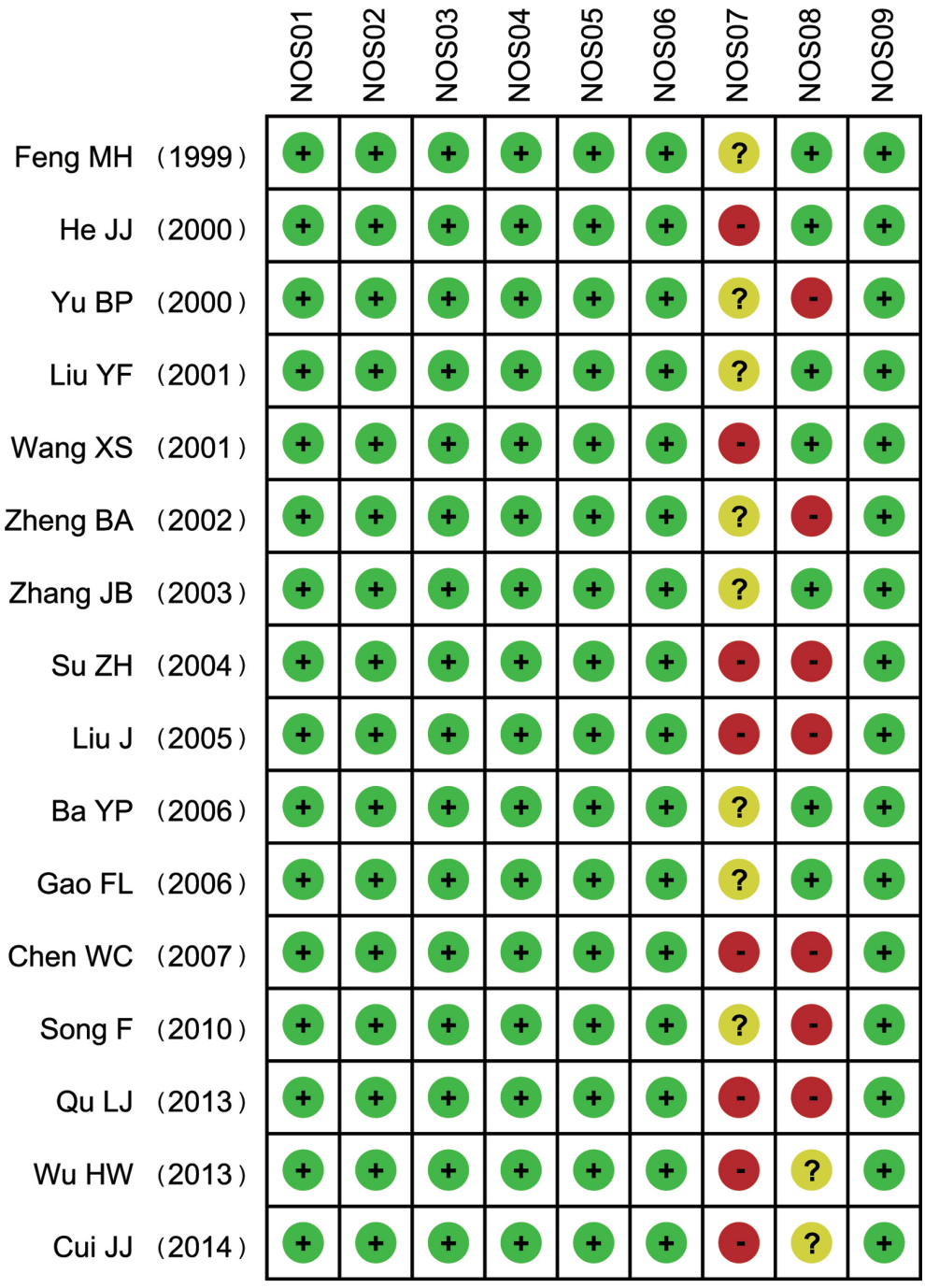
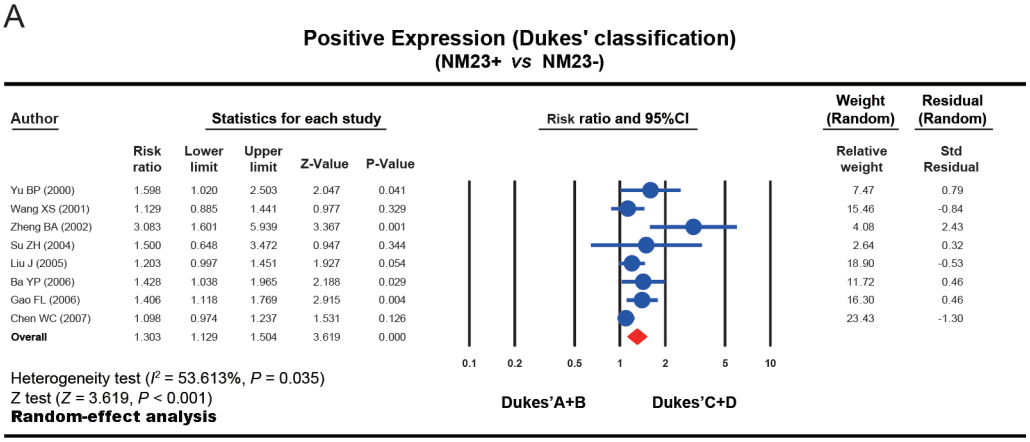


Figure 2. Newcastle-Ottawa Scale scores for the 16 eligible studies.

Meta-analysis of association between NM23 protein expression and CRC pathological characteristics

The correlation between NM23 protein expression and the pathological features of CRC was investigated in 12 studies. Heterogeneity was observed and thus the random-effect model was applied in the present study (Dukes staging: I^2 = 53.613%, P_h = 0.035; histological types: I^2 = 59.846%, P_h = 0.004). Higher NM23 protein expression was observed in patients with Dukes stage A and B than in patients with Dukes stage C and D (RR = 1.303, 95%CI = 1.129-1.504, P < 0.001). In addition, the NM23 protein was expressed at a higher level in well- and moderately differentiated tumors than in poorly differentiated tumors (RR = 1.369, 95%CI = 1.145-1.637, P = 0.001) (Figure 3).

A



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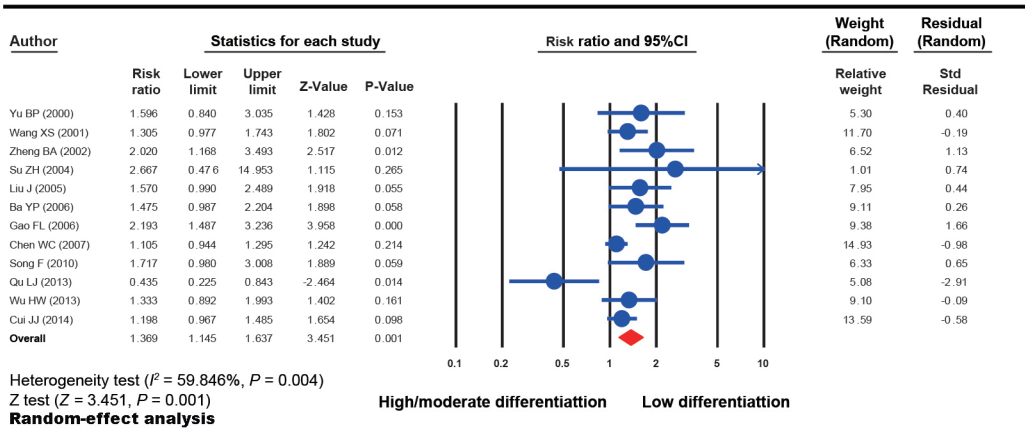

Figure 3. Forest analyses for the correlation between NM23 expression and pathological characteristics of colorectal cancer among Asians.

Meta-analysis of association between NM23 protein expression and CRC prognosis

The correlation between NM23 protein expression and CRC prognosis was reported in 7 studies. No heterogeneity was found in the 5-year survival rate and 5-year tumor relapse and the occurrence of metastasis (5-year survival rate: I^2 = 19.737%, P_h = 0.279; 5-year tumor relapse and metastasis: I^2 = 3.76%, P_h = 0.354); therefore, the fixed-effect model was applied. However, the random-effect model was used when heterogeneity was observed for the positive expression of the NM23 protein before and after 5-year survival (I^2 = 93.585%, P_h < 0.001). The results showed that the 5-year survival rate was higher in NM23-positive CRC patients than in NM23-negative CRC patients (RR = 1.862, 95%CI = 1.560-2.222, P < 0.001). Five-year tumor relapse and metastasis rates were lower in NM23-positive CRC patients than in NM23-negative CRC patients (RR = 0.516, 95%CI = 0.419-0.634, P < 0.001). However, there was no significant difference in NM23 protein expression between CRC patients with ≥5-year survival and CRC patients with <5-year survival (RR = 1.139, 95%CI = 0.960-1.352, P = 0.271) (Figure 4).

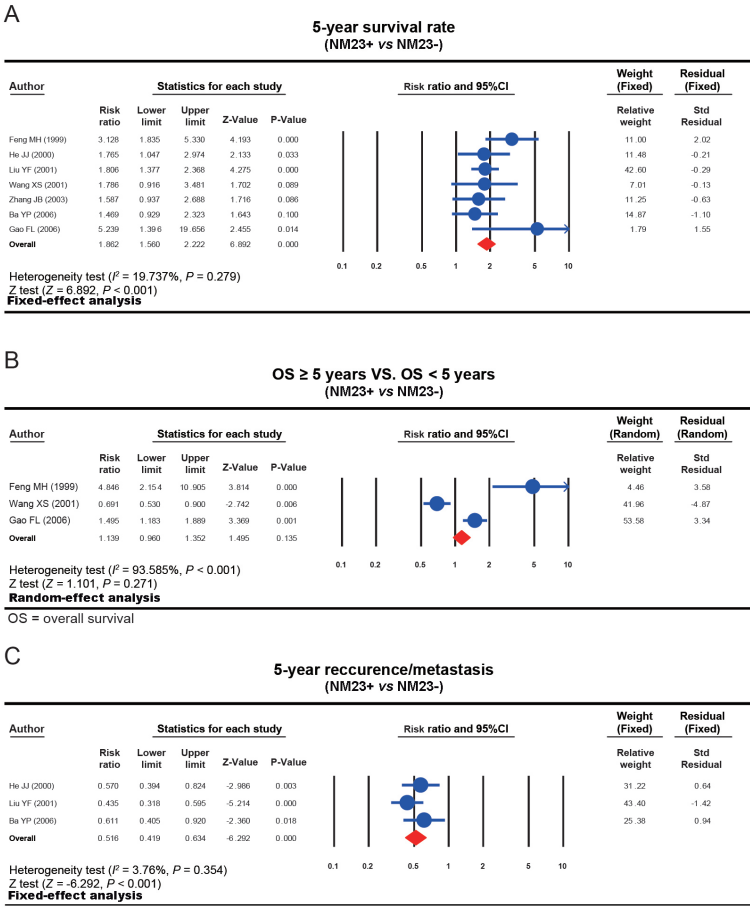

Figure 4. Forest analyses for the correlation between NM23 expression and prognosis of colorectal cancer among Asians.

Sensitive analysis and publication bias

Sensitivity analyses showed that no single study significantly affected the overall estimate of the correlation between NM23 expression, tumor pathology, and prognosis of CRC (Figure 5). Moreover, we found no obvious asymmetry in the shape of the funnel plots. The Egger regression test confirmed the absence of publication bias (P > 0.05).

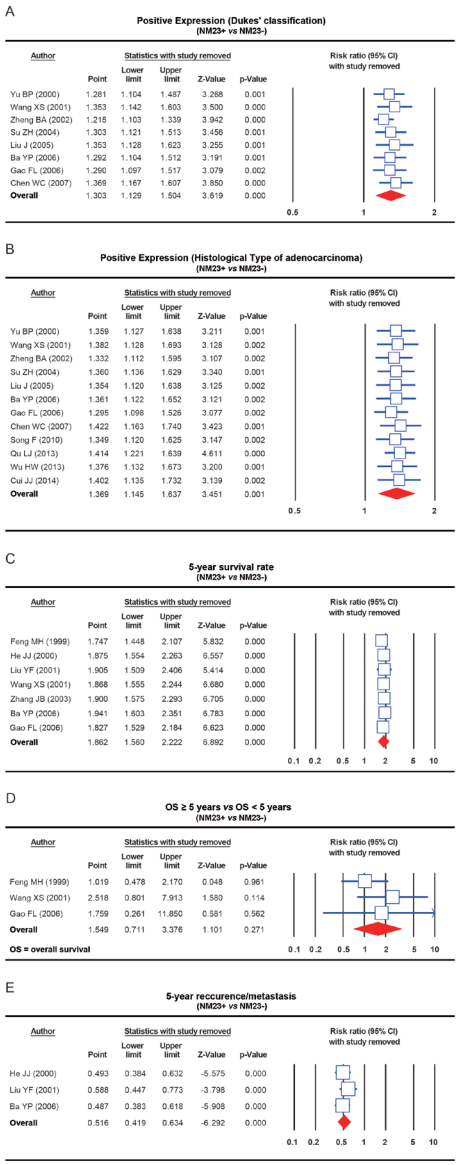

Figure 5. Sensitivity analysis on the correlation between NM23 expression, tumor pathology, and prognosis of colorectal cancer in Asians.

DISCUSSION

Meta-analysis of 16 randomized cohort studies revealed that NM23 expression is associated with tumor pathology in CRC in Asians. A higher NM23 protein expression level was observed in patients with Dukes stage A and B than in patients with Dukes stage C and D. The NM23 protein was also expressed at higher levels in moderately differentiated tumors than in poorly differentiated tumors. NM23 is a nucleoside diphosphate kinase and also has other enzymatic activities such as histidine kinase, transcriptional activation, and exonuclease activities (Marino et al., 2012). *NM23-H1* is well known for its ability to regulate distinct cellular functions (Lin et al., 2014). NM23 family proteins are involved in multiple-biological processes, such as cell differentiation, adhesion, migration, microtubule polymerization, signal transduction pathway, vascular invasion, and endocytosis, as well as tumor cell shape and apoptosis (Lin et al., 2014). The stage of local confinement of a tumor and the presence or absence of metastases, combined with other specific prognostic and predictive factors, are very important for patient management (Obrocea et al., 2011). Mutations, deletions, and altered expression of NM23 protein family members were found to be closely related to the metastatic capacity of many malignant tumors, including CRC (Wu et al., 2013). There is evidence to support an intracellular role for NM23 in tumor metastasis, such as in CRC (Wu et al., 2013). The NM23 protein is highly conserved from bacteria to humans and contributes substantially to the metastatic process by reducing NM23 protein expression in metastatic lymph nodes, indicating that metastatic tumor cells originate from and are mainly composed of cells with low NM23 expression. Data from several studies included in our meta-analysis showed that NM23 expression levels were correlated with the pathological characteristics of CRC. Our results strongly support that NM23 expression status is associated with the origin and development of CRC in Asians.

Another crucial result in our study is that NM23 expression may be used as a prognostic indicator of CRC among Asians. *NM23* was the first identified metastasis suppressor gene and its expression was found to be correlated with decreased metastatic capacity of tumor cells (Marino et al., 2012). The findings of this study also revealed a higher 5-year survival rate in NM23-positive CRC patients than in NM23-negative CRC patients. Five-year tumor relapse and metastasis were observed at a lower rate in NM23-positive CRC patients than in NM23-negative CRC patients, suggesting that NM23 is positive indicator of a favorable CRC prognosis. Previous studies have shown that NM23 protein levels were correlated with the progression of CRC and could be used as an index for predicting invasion and metastasis potential (Liu et al., 2011; Wu et al., 2013). Our results support those of previous studies and further suggest that high NM23 levels are correlated with a better prognosis, and thus NM23 expression can be used as a reliable and independent prognostic indicator in CRC.

There were several limitations in our meta-analysis. Briefly, some of the studies included had relatively small sample sizes. Moreover, selection and language bias may have existed in this meta-analysis because only studies published in English and Chinese languages were used. Furthermore, all 16 studies selected were conducted in China, and thus geographical coverage was limited in identifying ethnic differences among Asian populations when determining the correlation between NM23 expression, tumor pathology, and prognosis of CRC. Further studies should be conducted in other populations to represent a more heterogeneous Asian population to confirm our findings.

In conclusion, we found strong correlations between NM23 expression, tumor pathology, and prognosis of CRC in Asians. Further studies including larger sample sizes focused on Asian populations will contribute to the reliability of our results and validate NM23 as a reliable biomarker for assessing CRC behavior.

Conflicts of interest

The authors declare no conflict of interest.

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