

## Original Article

# Serum CD26 levels may be correlated with the risk of colorectal cancer among Asian populations: a meta-analysis

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**Abstract:** Objective: This meta-analysis aims to investigate the association between serum CD26 levels and the risk of colorectal cancer (CRC). Methods: Potential relevant studies were searched through electronic databases. Case-control studies were selected for assessing the association between serum CD26 levels and the risk of CRC, and extracted data were analyzed by using the Comprehensive Meta-analysis (version 2.0) software. A fixed-effect model or random-effect model was used for calculating the standardized mean difference (SMD) with its corresponding 95% confidence interval (CI) to investigate the association between serum CD26 levels and the risk of CRC. Results: Seven case-control studies were selected with a total of 1,571 subjects (containing 714 CRC patients and 857 healthy controls). Negative association was found between serum CD26 levels and the risk of CRC (SMD = -0.334, 95% CI: -2.967~2.299,  $P = 0.803$ ). Ethnicity-subgroup analysis showed that serum CD26 levels may be related to the risk of CRC among Asian populations (SMD = 3.939, 95% CI: 1.553~6.325,  $P = 0.001$ ), while no significant difference was found among Caucasian populations (SMD = -3.774, 95% CI: -7.670~0.123,  $P = 0.058$ ). Conclusion: These results indicate that serum CD26 levels may be related to CRC among Asian populations.

**Keywords:** CD26, serum level, colorectal cancer, meta-analysis, Asian populations

## Introduction

Colorectal cancer (CRC) remains the third leading cause of cancer deaths in both men and women [1]. In 2012, it was estimated that CRC brought about approximately 1,360,000 new diagnoses and about 694,000 deaths worldwide [2]. An estimated 20% of CRC patients are at far advanced stage at the time of diagnosis and have a 5-year survival rate of only 12% [3]. The factors associated with CRC are controversial and complex, and non-genetic risk factors include older age, male gender, high intake of fat, alcohol or red meat, obesity, smoking and a lack of physical exercise [4]. Besides, studies show that intake of cereal fibers is more strongly related with the decrease of CRC risk, and the unhealthy patterns of diet and lifestyle are also regarded as the leading factors for CRC risk [1, 5]. Furthermore, some previous studies demonstrated that genetic factors also affect-

ed CRC epidemic [6, 7], and serum CD26 level was reported as an important biomarker involved in the risk of CRC [8].

CD26, a membrane-anchored cell surface peptidase, is also known as a highly glycosylated type II membrane sialoglycoprotein consisting of 766 aminoacids, which is capable of transmitting intracellular signals through a short intracellular tail and usually exists in the circulation as a second smaller soluble form [8]. Generally, CD26 is expressed in various types of haematopoietic cells, such as endothelial cells, fibroblasts, activated B and T lymphocytes and natural killer cells; and it is also frequently observed in epithelial cells of different tissues, including the lung, liver, kidney, intestine, prostate, and placenta [9, 10]. Recently, serum levels of CD26 have been reported to be closely correlated with the etiology of CRC, and CD26 expressed in the neoplastic colon cell

membrane may possess the ability to modulate tumor growth and dissemination [8, 11]. Furthermore, CD26 can interact with other proteins, such as collagen, caveolin-1, and fibronectin, to participate in the process of cell motility and invasion [12, 13]. More importantly, it has been postulated that the interaction of CD26 with an unknown putative ligand might lead to a continuous activation of NF-kappa B, thereby resulting in the uncontrolled growth of colorectal cells [14]. Previous study also revealed that there was strong positive correlation between serum levels of CD26 and the risk of CRC, suggesting that CD26 might be utilized as a serum marker in the diagnosis and prognosis of CRC [15]. However, other epidemiological studies also illustrated contradictory findings with regard to the relationship between serum CD26 levels and the risk of CRC development [14, 16]. Therefore, the current meta-analysis aggregated reliable data and results from relevant studies in order to identify the possible association between serum CD26 levels and the risk of CRC.

### Materials and methods

#### *Data sources and keywords*

We thoroughly searched several databases, like PubMed, Web of Science, Embase, China BioMedicine (CBM), Cochrane Library, Wanfang database and China National Knowledge Infrastructure (CNKI) using a combination of free words and keywords with a retrieval range from the day the database was built to May 30th, 2016 in order to identify studies concerning the correlations between serum CD26 levels and the risk of CRC. For the keywords used in our search, we selected (“Dipeptidyl Peptidase 4” or “DPP4 protein, human” or “Dipeptidyl-Peptidase IV” or “Dipeptidyl Peptidase IV” or “Dipeptidyl-Peptidase 4” or “CD26 Antigen” or “CD26” or “Adenosine Deaminase Complexing Protein 2” or “CD26 Antigens” or “DPP-IV” or “dipeptidylpeptidase 4” or “ADCP2”) for the exposure factors, and (“Colorectal Neoplasms” or “Colonic Neoplasms” or “Rectal Neoplasms” or “Colorectal Neoplasms” or “Colorectal Tumor” or “Colorectal Carcinoma” or “Colorectal Cancer” or “large intestine cancer” or “large intestine carcinoma” or “large intestinal cancer” or “large intestinal carcinoma” or “large bowel cancer” or “large colon cancer” or “intes-

tinal cancer” or “intestinal carcinoma” or “intestinal neoplasms” or “intestine cancer” or “intestine carcinoma” or “intestine neoplasms” or “bowel carcinoma” or “bowel cancer” or “bowel neoplasms” or “Colonic Neoplasms” or “Colonic Tumor” or “Colonic Carcinoma” or “Colonic Cancer” or “Colon Neoplasms” or “Colon Tumor” or “Colon Carcinoma” or “Colon Cancer” or “Rectal Neoplasms” or “Rectal Tumor” or “Rectal Carcinoma” or “Rectal Cancer” or “Rectum Neoplasms” or “Rectum Tumor” or “Rectum Carcinoma” or “Rectum Cancer”) for the outcome factors.

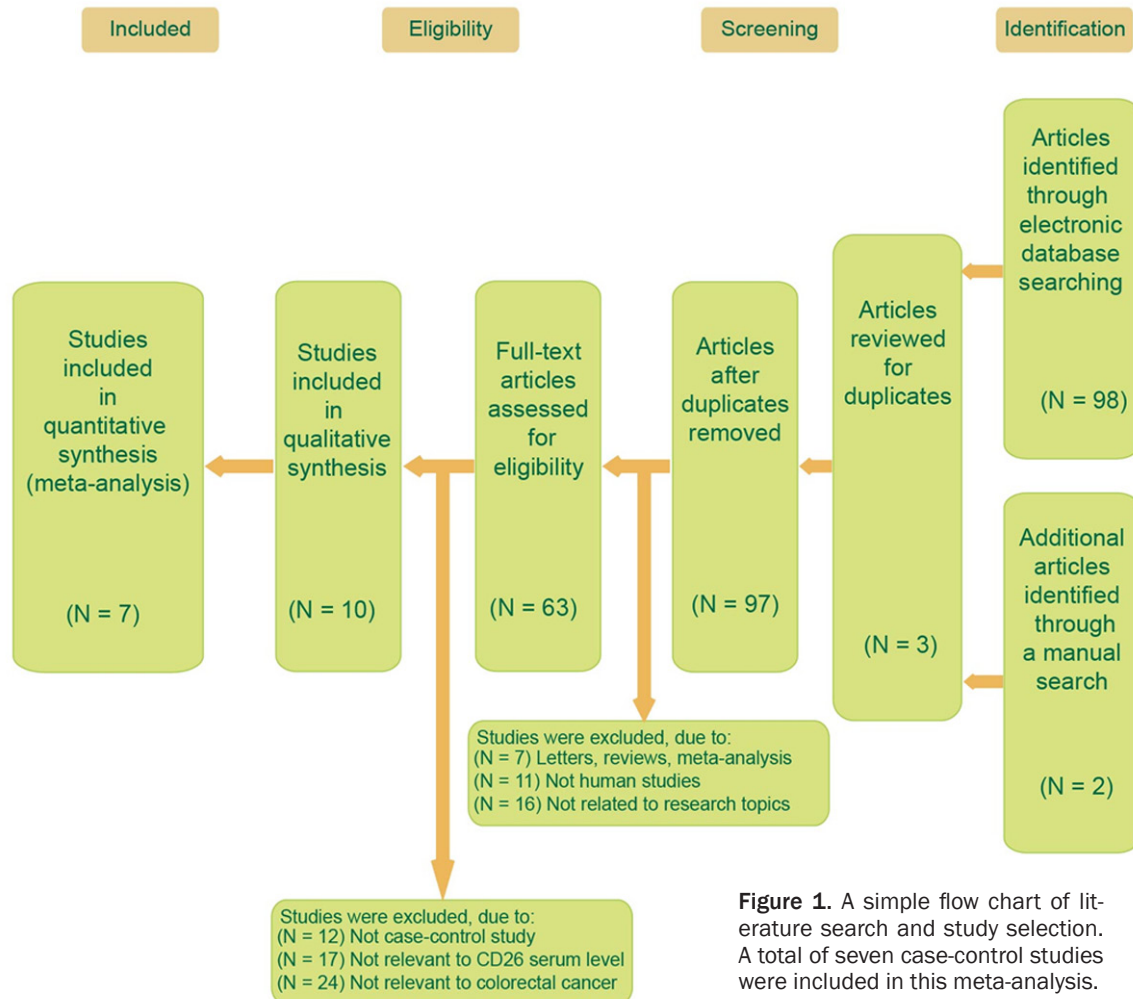
#### *Selection criteria*

Studies were included if they met the following criteria: (1) study types: case-control study about the correlation between serum CD26 levels and the risk of CRC; (2) study subjects: patients diagnosed with CRC and confirmed by pathological examination; (3) outcomes: serum levels of CD26 in CRC patients and healthy controls. Besides, studies would be excluded if: (1) studies only had reviews and/or abstract; (2) studies were animal studies; (2) studies were papers repeatedly published; (3) studies had poor data integrity. If the extracted studies were published by the same authors with the same case data, only the latest one or the largest sample size was included.

#### *Data extraction and quality assessment*

Based on a predefined form, two investigators extracted all relevant information independently. The following relevant information were abstracted from all the included studies: first author, publication year, country, ethnicity, source of controls, sample size, gender, age, detection method of serum CD26 levels, and fecal serum levels of CD26. The quality evaluation of enrolled studies was performed by two or more investigators, using the Newcastle-Ottawa Scale (NOS) criteria [17]. The details of NOS criteria containing the following aspects: Whether the case definition adequate or had independent validation (NOS01)? Whether the case had representativeness (NOS02)? Whether the controls were community controls (NOS03)? Whether the controls had no history of disease or endpoint (NOS04)? Whether the study controls the most important factor (NOS05)? Whether the study controls any additional factors (NOS06)? Whether there was

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**Figure 1.** A simple flow chart of literature search and study selection. A total of seven case-control studies were included in this meta-analysis.

secure record for exposure (NOS07)? Whether the blind method was used (NOS08)? Whether the same method was used for ascertainment for cases and controls (NOS09)? Whether the non-response rates were the same in two groups (NOS10)?

### Statistical analysis

A fixed-effect model or a random-effect model was used for calculating the standardized mean difference (SMD) with its corresponding 95% confidence interval (CI) to investigate the correlations between serum CD26 levels and the risk of CRC. Besides, Z test was conducted to identify the significance of pooled SMDs [18]. Forest plot was also drawn to reflect the SMD and its 95% CI after comparison between two groups. Cochran's Q test was used for testing the heterogeneity [19], and  $P_h < 0.05$  presented the existence of the heterogeneity.

Besides,  $I^2$  test (0%~100%, the higher the  $I^2$  value is, the more obvious the heterogeneity will be) was conducted for measuring heterogeneity. If  $P_h < 0.05$  or  $I^2 > 50\%$ , there was great heterogeneity among studies, and a random-effects model would be conducted; otherwise, a fixed-effects model was used [20]. We also conducted the sensitivity analysis to assess whether the deletion of one single study would change the overall outcomes. Funnel plot, classic fail-safe N and Egger's linear regression test were performed for the assessment of the existence of publication bias to guarantee the reliability of the results [21-23]. A P value of  $< 0.05$  was deemed as statistically significant. Meta regression analysis was conducted for assessing the possible sources of heterogeneity, and Monte Carlo simulation was applied for multiple calibration tests [24-26]. To make sure the credibility and accuracy of the results, Com-

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**Table 1.** Baseline characteristics of included studies

First author	Year	Country	Ethnicity	Publish Language	Source of controls	Number		Gender (M/F)		Age (years)	
						Case	Control	Case	Control	Case	Control
Wang XG-a	2012	China	Asians	Chinese	Health sample	59	41	36/23	20/21	56.0 ± 13.0	58.0 ± 12.0
Wang XG-b	2012	China	Asians	Chinese	Benign sample	59	51	36/23	22/29	56.0 ± 13.0	54.0 ± 14.0
Tao S-a	2012	Germany	Caucasians	English	Health sample	179	225	98/81	100/125	-	-
Tao S-b	2012	Germany	Caucasians	English	Benign sample	179	193	98/81	124/69	-	-
Bunger S	2012	Germany	Caucasians	English	Health sample	164	119	96/68	52/67	69.59 (40.5~99.1)	62.41 (19.5~90.8)
Guo LW	2011	China	Asians	Chinese	Health sample	120	60	72/48	40/20	48.2	43.6
Wu HP	2010	China	Asians	Chinese	Health sample	60	30	36/24	20/10	47.2 (22~70)	42.6 (21~55)
De Chiara	2010	Spain	Caucasians	English	Health sample	33	68	-	-	18~93	18~93
De la Haba-Rodriguez J	2002	Spain	Caucasians	English	Health sample	99	70	61/38	40/30	62 (34~78)	58 (33~71)

M: male; F: female.

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	NOS01	NOS02	NOS03	NOS04	NOS05	NOS06	NOS07	NOS08	NOS09	NOS10
Wang XG-a (2012)	+	+	+	+	+	+	+	?	+	+
Wang XG-b (2012)	+	+	+	+	+	+	+	?	+	+
Tao S-a (2012)	+	+	+	+	+	+	+	+	?	+
Tao S-b (2012)	+	+	+	+	+	+	+	+	?	+
Bunger S-a (2012)	+	+	+	+	+	+	+	+	+	?
Bunger S-b (2012)	+	+	+	+	+	+	+	+	?	+
Guo LW (2011)	+	+	+	+	+	+	+	-	+	+
Wu HP (2010)	+	+	+	+	+	+	+	+	?	+
De Chiara L-a (2010)	+	+	+	+	+	+	+	+	?	+
De Chiara L-b (2010)	+	+	+	+	+	+	?	+	?	+
Haba-Rodriguez J (2002)	+	+	+	+	+	+	+	+	+	?

**Figure 2.** The assessment of the methodological quality of seven case-control studies was carried out using the NOS scores.

prehensive Meta-analysis 2.0 (Biostat Inc., Englewood, New Jersey, USA) software was adopted for statistical analysis.

### Results

#### Included studies

A total of 100 articles regarding the correlation of serum CD26 levels with the risk of CRC were initially selected through screening the titles and key words. Totally 37 studies were removed for the following reasons: 3 for duplicates, 7 for reviews, letters, or meta-analysis, 11 for non-human studies, as well as 16 for not related to research topics. The left 63 studies were further reviewed and 12 studies were excluded for not case-control studies, 17 for not relevant to serum CD26 levels and 24 for not relevant to CRC. Finally, 7 papers were enrolled in our meta-analysis and 3 studies were removed for not supplying enough information. These 7 studies were 3 in Asian populations and 4 in Caucasian populations, including 1,571 subjects altogether (containing 714 patients with CRC and 857 healthy controls), and the publication time of the enrolled studies were between 2002 and 2012 [8, 14, 15, 27-30]. Among those 7 studies, 3 studies were performed in China, 2 studies in Germany and 2 studies in Spain. Sources of controls in our

present study were healthy samples and/or benign samples. The only method used to detect serum CD26 levels in this current meta-analysis was Enzyme-Linked Immunosorbent Assay (ELISA). Additionally, as for screening, a flow chart of the selection process of all the enrolled studies is displayed in **Figure 1**. The baseline characteristics of included studies are shown in **Table 1** and the methodological quality of the extracted studies is displayed in **Figure 2**.

#### Primary results of meta-analysis

As shown in **Figure 3**, the major results of the current meta-analysis revealed a negative association between serum CD26 levels and the risk of CRC (SMD = -0.334, 95% CI: -2.967~2.299,  $P = 0.803$ ). Subgroup analysis based on ethnicity implied that serum CD26 levels might be the primary risk factor for CRC in Asian populations (SMD = 3.939, 95% CI: 1.553~6.325,  $P = 0.001$ ), while no significant difference was found in Caucasian populations (SMD = -3.774, 95% CI: -7.670~0.123,  $P = 0.058$ ) (**Figure 4A**). Further subgroup analyses based on sources of controls showed that serum CD26 levels were negatively correlated with the risk of CRC both in benign samples and healthy samples (benign sample: SMD = -1.598, 95% CI: -15.081~11.884,  $P = 0.816$ ; health sample: SMD = 0.023, 95% CI: -2.521~2.567,  $P = 0.986$ ) (**Figure 4B**). Subgroup analyses based on published language were also conducted. The results showed that serum CD26 levels were correlated with risk factor of CRC in the Chinese studies (SMD = 3.939, 95% CI: 1.553~6.325,  $P = 0.001$ ), while no significant correlation was found in the English studies (SMD = -3.774, 95% CI: -7.670~0.123,  $P = 0.058$ ) (**Figure 4C**).

#### Sensitivity analysis and publication bias

The results of sensitivity analysis showed no influence on the pooled SMD in the correlation between serum CD26 levels and the risk of CRC (**Figure 5**). No asymmetry was observed in

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## Serum CD26 level(Case vs. Control)

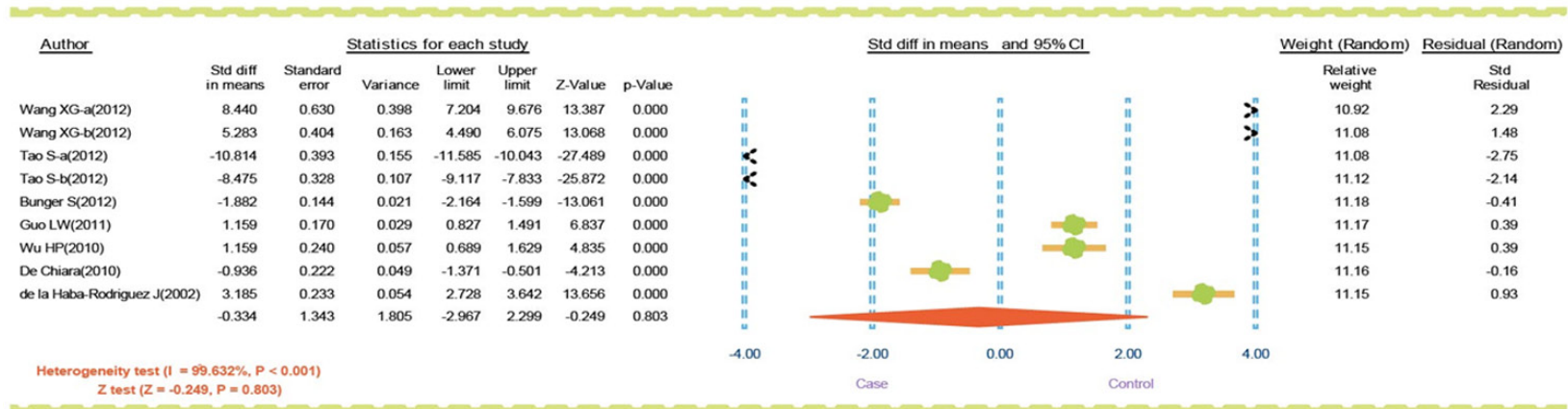
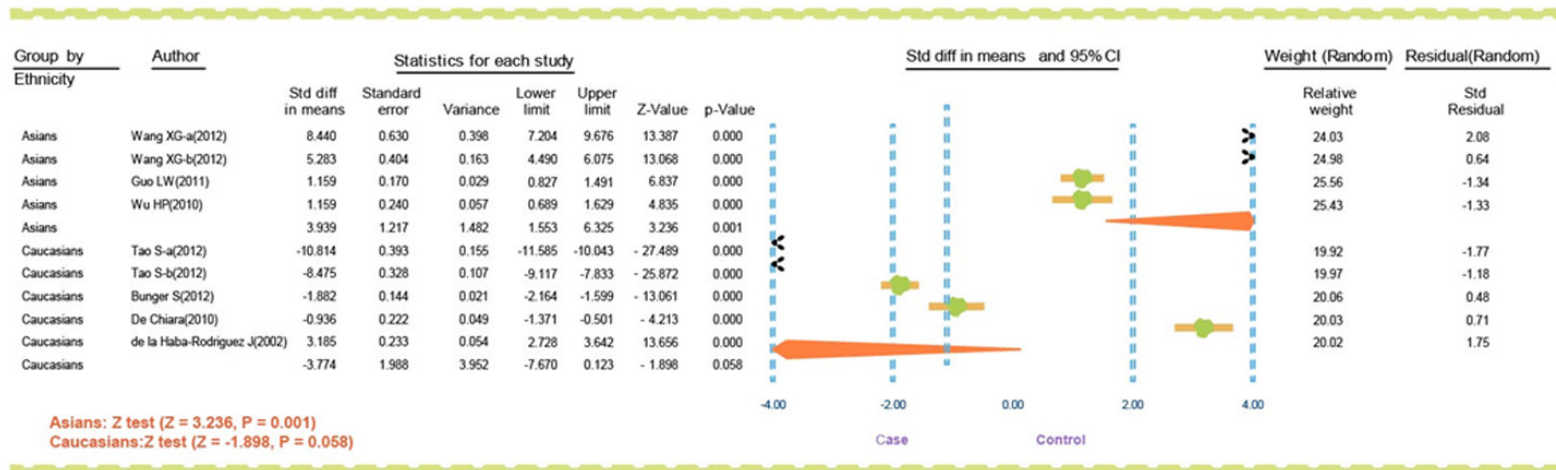


Figure 3. Forest plots of seven case-control studies on the difference of serum CD26 levels between colorectal cancer and healthy subjects.

A

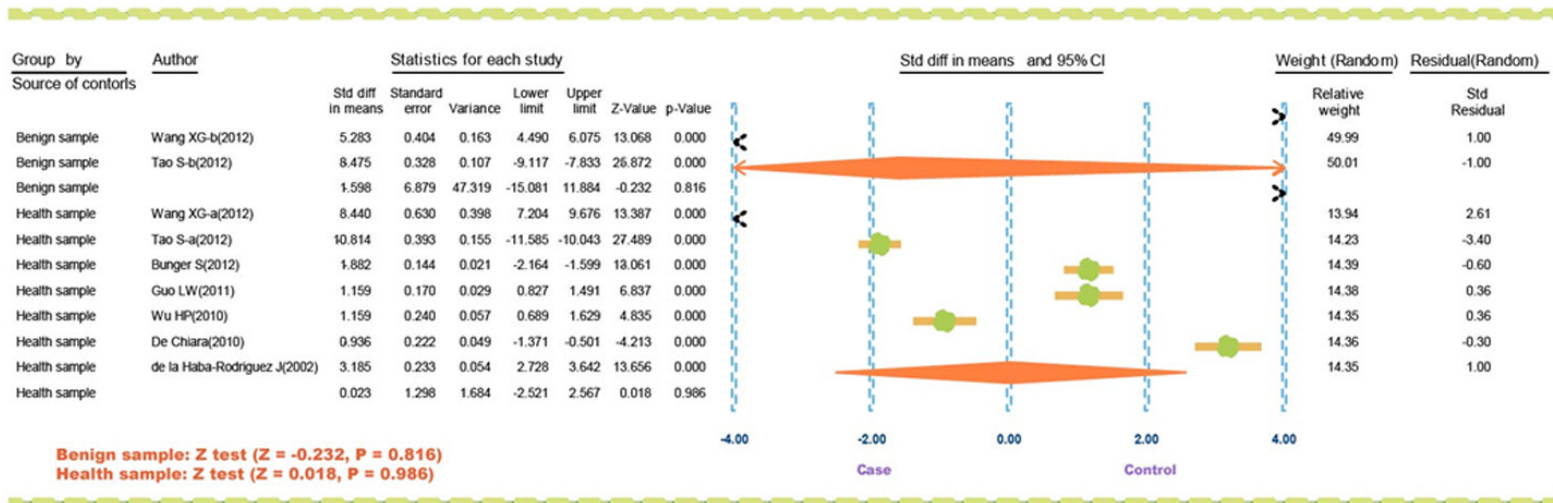
## Serum CD26 level (Ethnicity: Case vs. Control)



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B

### Serum CD26 level(Source of controls: Case vs. Control)



C

### Serum CD26 level(Language: Case vs. Control)

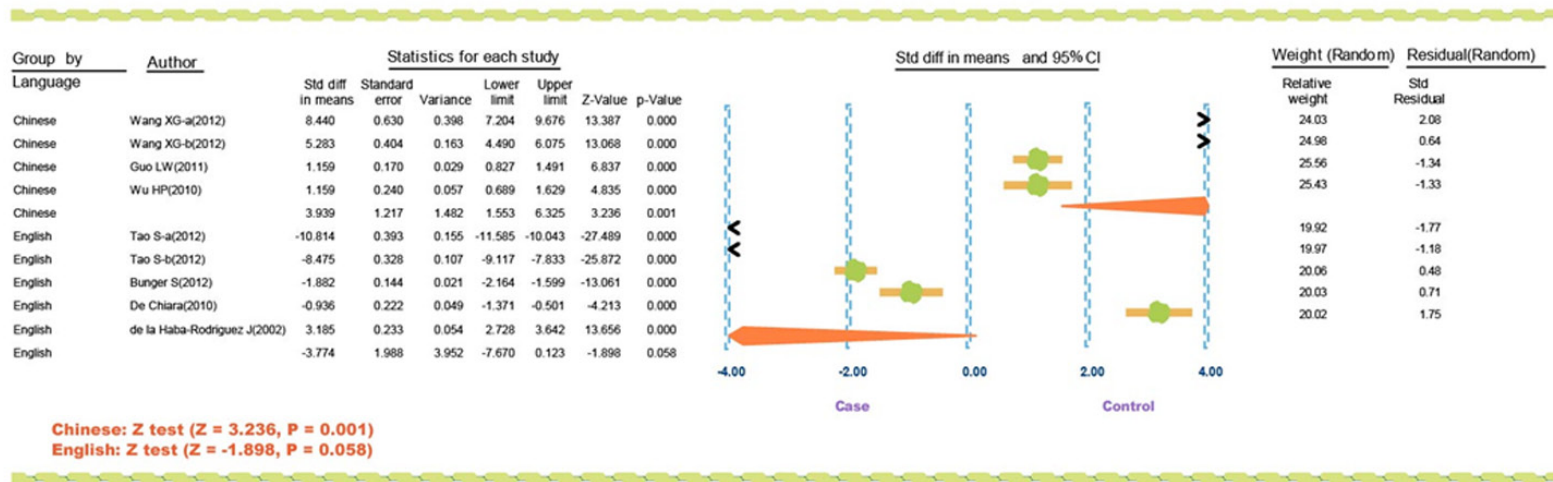
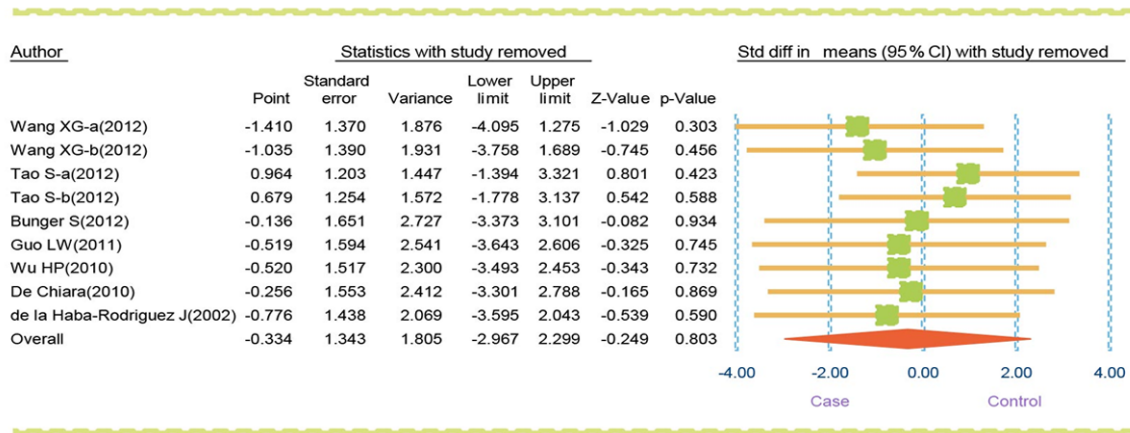


Figure 4. Subgroup analyses of seven case-control studies on the difference of serum CD26 levels between colorectal cancer and healthy subjects.

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**Figure 5.** Sensitivity analyses of seven case-control studies on the difference of serum CD26 levels between colorectal cancer and healthy subjects.

the funnel plots, and the results showed no existence of publication bias in this present meta-analysis. Additionally, classic fail-safe N analysis together with Egger's test further proved no existence of publication bias in our meta-analysis (all  $P > 0.05$ ) (**Figure 6**). Meta regression analysis results showed that ethnicity, sources of control, language, country, sample size and publish year were not the main sources of heterogeneity and were not the key factors influencing total effect value (all  $P > 0.05$ ) (**Figure 7**).

### Discussion

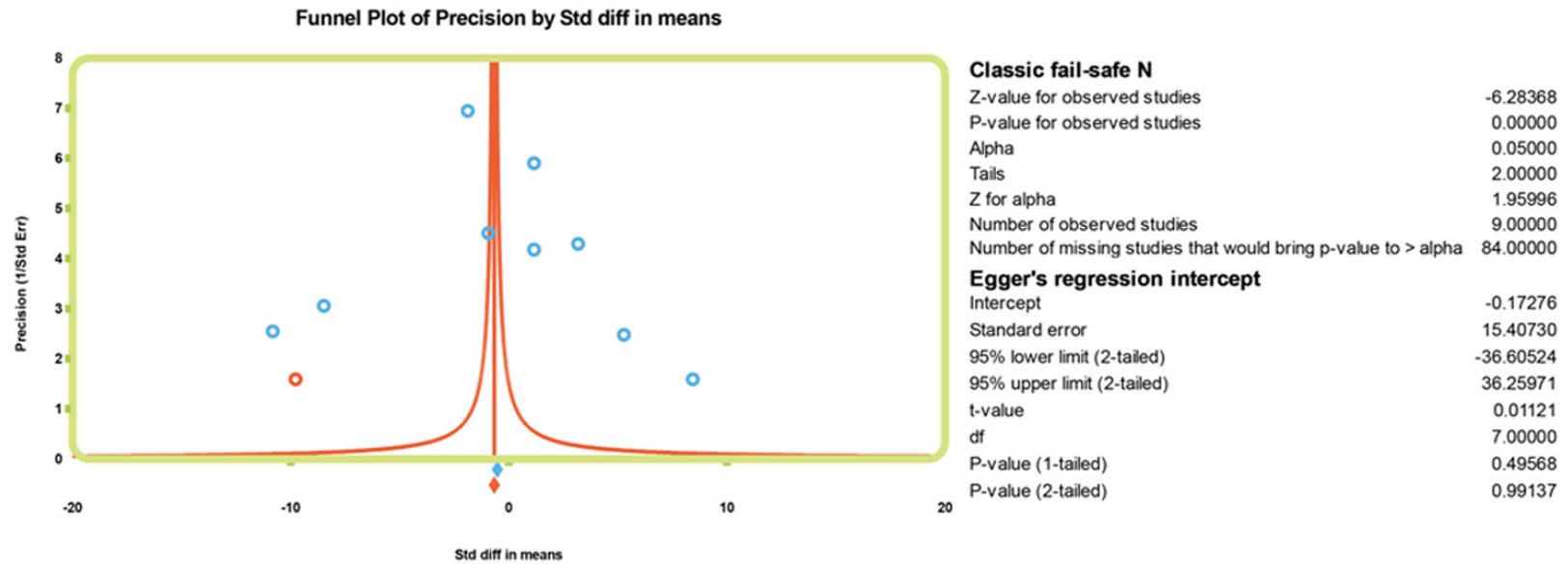
In this meta-analysis, we intended to investigate the association between the serum CD26 levels and the risk of CRC. The main results of this meta-analysis revealed that negative association was found between serum CD26 levels and the risk of CRC, while ethnicity-subgroup analysis showed that serum CD26 levels may be related to the risk of CRC in Asian populations, implying that serum CD26 levels may be closely connected with the progression of CRC, and also the CD26 levels can act as a potential serum marker for the early diagnosis of CRC. CD26 is considered to be a highly glycosylated type II transmembrane glycoprotein, which is composed of two homologous subunits and has totally 766 amino acids [31]. Furthermore, CD26 is regarded as a multi-functional protein that is mainly expressed in the epithelial cells, endothelial cells and lymphocytes and it can also act as a soluble protein released into cytoplasm [32]. It is worthwhile to note that CD26 may be expressed in various hematopoietic

cells, such as activated T lymphocytes, natural killer cells, fibroblasts and other cells, which are involved in the migration process [9]. CD26 has been implicated in the immunological regulation, signal transduction and cell apoptosis, and also plays a vital role in the development/progression of neoplasms [33]. Besides the regulatory role in the progression and neoplastic transformation process of CRC, CD26 also plays a crucial role in tumor migration and tumor metastasis due to its ability to combine extracellular matrix proteins [34]. In line with our study results, Lam *et al.* have showed the development of CRC has close relationship to the serum CD26 levels [35]. A previous study carried out by De Chiara *et al.* has revealed that serum CD26 levels can serve as a useful serum marker for the progression of CRC [8].

Additionally, stratified analyses on the basis of the ethnicity, sources of controls and publish language were performed. Subgroup analysis based on ethnicity showed that serum CD26 level has a positive association with the progression of CRC among Asian populations, while the serum CD26 levels were negatively related to the progression and prognosis of CRC among Caucasian populations, implying that ethnicity difference may be one of the potential heterogeneity sources of these results. These diametrically opposite outcomes in different ethnicity may be caused by the interaction among different geographical environment, genetic differences, and different risk factors of fundamental lifestyle.



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**Figure 6.** Funnel plots, Classic fail-safe N analysis and Egger's test of publication biases on the difference of serum CD26 levels between colorectal cancer and healthy subjects.

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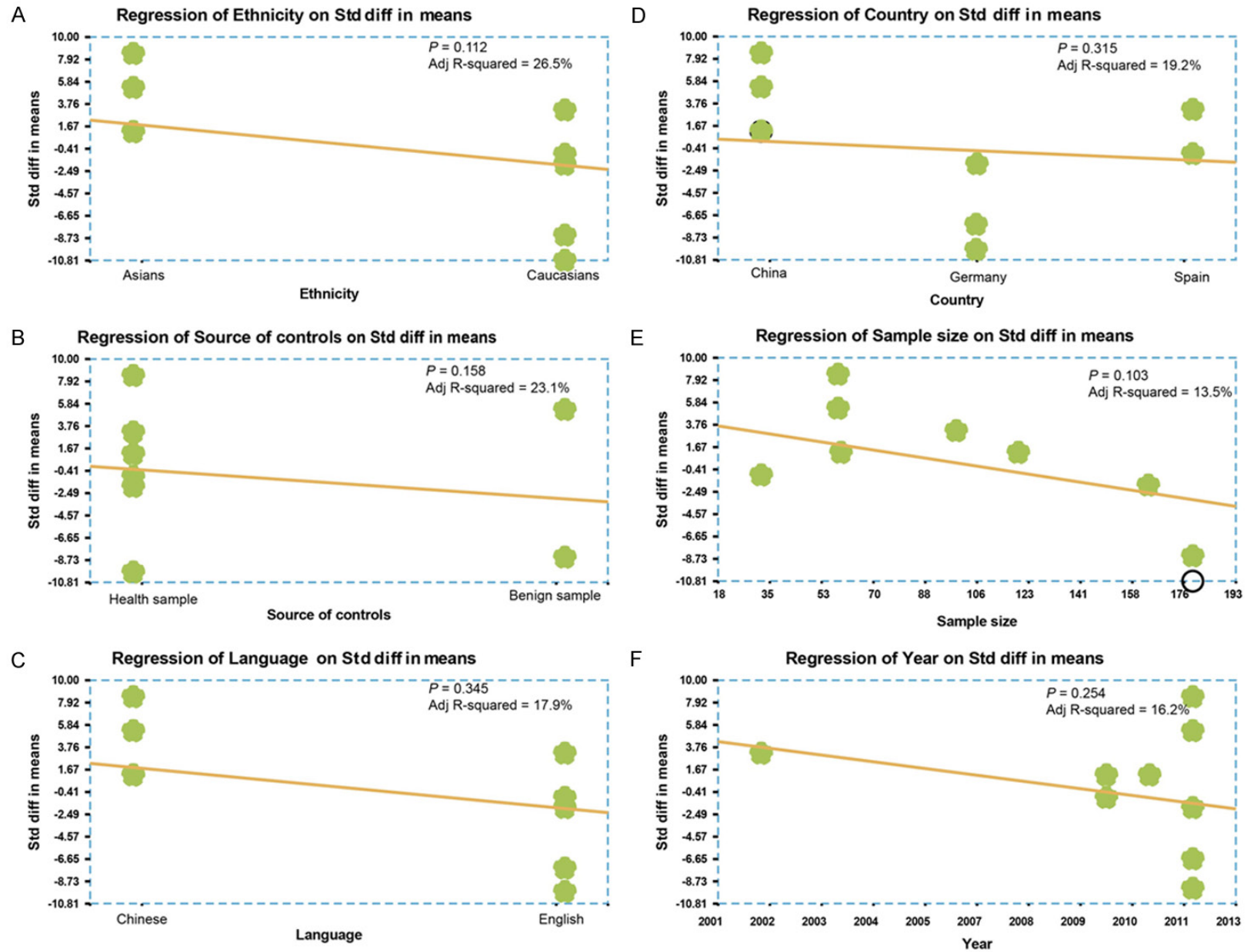


Figure 7. Meta regression analysis based on ethnicity, sources of control, language, country, sample size and publish year.

The major results of the meta-analysis revealed a negative association between serum CD26 levels and the risk of CRC, which is different from the results obtained from other studies. The negative results might be caused by the following limitations: Firstly, only 7 papers concerning our topic were enrolled, which might cause bias for the final outcomes; secondly, all participants involved in this study might undergo no uniform diagnostic criteria for CRC, such as colonoscopy, which would have a negative effect on our results; thirdly, some of these included studies were recruited with a relatively small numbers of CRC patients, which would influence the assessment of test sensitivity for detecting CRC. Furthermore, serum CD26 levels were measured not qualitatively in this study (high or decrease; positive or negative), which may be another limitation ignoring the exploration of quantitative data that restrict the present results. All of the mentioned limitations above could eventually cause an inconsistent outcome.

Taken together, our results show that serum CD26 levels may be related to the risk of CRC in Asian populations. The potential use of CD26 and other blood-based tests together with more markers might deserve further attention. However, due to the limitations in the sample size and study design of enrolled studies, future detailed studies with more specific data, information and larger populations are required for a comprehensive analysis of the association between serum CD26 levels and the risk of CRC.

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### Disclosure of conflict of interest

None.

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