Plasma von Willebrand factor levels in patients with cancer: A meta-analysis

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Abstract. von Willebrand Factor (VWF) is well recognized for being dysregulated in various malignancies and has emerged as a potential biomarker for cancer detection. The present meta-analysis aimed to elucidate the association between plasma VWF and the incidence and metastasis of cancer. For this purpose, a comprehensive search was conducted across multiple databases from their inception until March 3, 2023. This culminated in the selection of 15 original studies on various types of cancer, including a collective sample of 1,403 individuals. The standardized mean difference (SMD) and 95% confidence intervals (CIs) were employed as statistical parameters to determine the association between plasma VWF and the incidence and metastasis of cancer. These were estimated using a random-effects model. The pooled data revealed that the plasma VWF levels of patients with cancer were significantly elevated compared with those of healthy controls (SMD, 0.98; 95% CI, 0.59-1.36), and a significant association was observed between plasma VWF levels and cancer metastasis (SMD, 0.69; 95% CI, 0.33-1.06). The symmetry of the Begg's funnel plots indicated that no significant bias was present in the analyses of VWF in cancer and its metastasis. In summary, the results of the present meta-analysis support the hypothesis that increased plasma VWF levels may serve as a biomarker for cancer and metastatic progression.

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Abbreviations: VWF, von Willebrand factor; SMD, standard mean difference; CI, confidence interval; EC, endothelial cell

Key words: VWF, plasma, cancer, meta-analysis

Introduction

von Willebrand factor (VWF) is a large, complex glycoprotein, predominantly synthesized in endothelial cells (ECs) and megakaryocytes (1,2). VWF is released via synthetic pathways or regulatory mechanisms associated with secretory storage and subsequent discharge (3,4). Although platelets also release VWF, plasma VWF mostly originates from ECs (5). A considerable quantity of VWF within ECs is compartmentalized in Weibel-Palade bodies, from which it is released into the vascular lumen in response to a range of stimuli (6,7). Once in the bloodstream, the primary function of VWF is to facilitate hemostasis. This is primarily accomplished by its strong interaction with platelet receptor glycoprotein Ib (GPIb) and various constituents of the subendothelial connective tissue (8,9). Furthermore, VWF binds to another clotting protein, factor VIII, and serves as its carrier in the blood circulation (10). Previous studies have demonstrated that VWF is a pivotal regulator in multiple biological processes. Specifically, VWF has been identified to contribute to the modulation of angiogenesis (11), inflammatory responses (12), cell proliferation dynamics (13) and apoptotic mechanisms (14).

The EC monolayer serves a critical function as a regulatory gateway for the ingress and egress of metastatic tumor cells. Disseminated tumor cells secrete an array of factors that directly instigate the activation of ECs, which is defined by the upregulation of distinct adhesion receptors and a concurrent increase in vascular permeability, thereby facilitating the transendothelial migration of tumor cells (15-19). In a study conducted by Bauer *et al* (20), malignant melanoma cells were demonstrated to induce EC activation, a phenomenon validated in controlled *in vitro* environments and within living organisms. The initiation of EC activation culminates in the increased secretion of VWF and the subsequent formation of ultra-large VWF multimers on the surface of the ECs (20). Previous studies have consistently indicated that VWF

enhances the attachment of melanoma and colon cancer cells to the endothelium under conditions of shear stress. This process is critical in promoting the metastasis of these tumor types (21-23).

Cancer is a growing burden on global health systems (24). It was forecast that in 2023 there would be ~1.96 million new cancer cases and 610,000 cancer-associated fatalities in the United States (25). Furthermore, it has been predicted that by 2040 there will be ~28.4 million new cancer cases worldwide, representing a 47% increase compared with the number of cases reported in 2020 (26). Evidence suggests that notable increases in VWF plasma levels occur in patients with various types of tumors (27,28). Wang *et al* (29) observed a significant increase in the VWF plasma levels of patients with colorectal cancer compared with healthy individuals. Moreover, another study of colorectal cancer indicated a direct association between heightened plasma VWF levels and tumor progression to advanced stages, as well as the presence of metastases (30). Notably, patients with colorectal cancer whose VWF levels were low exhibited a significantly extended survival time compared with those whose VWF levels were high (29). In addition, Yang *et al* (31) found that vascular endothelial growth factor derived from cancer cells promotes the metastasis of gastric adenocarcinoma. Research has also shown that VWF facilitates the adhesion between tumor cells and ECs, and assists in the recruitment of platelets to the tumor microenvironment (32). This leads to the formation of tumor-platelet aggregates, promoting the hematogenous dissemination of cancer.

However, findings contradictory to the aforementioned results have also been reported. Meschengieser *et al* (33) observed that patients with myeloproliferative tumors exhibited lower VWF levels compared with healthy individuals. In addition, Von Willebrand disease (VWD) is a condition typically caused by mutations in the VWF gene, which lead to reduced quantities or abnormal quality of VWF in the plasma (34). Franchini *et al* (34) analyzed the VWF levels in patients with VWD who also had various types of cancer, including liver cancer, breast cancer, non-Hodgkin lymphoma and acute myeloid leukemia, and identified no statistically significant differences in the data when comparing patients with metastatic cancer to those without.

The aim of the present meta-analysis was to assess whether VWF is consistently elevated in patients with cancer, determine its association with cancer metastasis and thereby evaluate its potential as an effective cancer biomarker.

Materials and methods

Search strategy. A systematic examination of the literature was undertaken, encompassing various databases including The Cochrane Library (https://www.cochranelibrary.com/library), PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Web of Science (https://www.webofscience.com), China National Knowledge Infrastructure (https://www.cnki.net) and Wanfang Data (http://www.wanfangdata.com), to ensure a thorough analysis. The study included case-control investigations published from database inception until March 3, 2023, which presented findings regarding plasma VWF concentrations in patients with cancer compared with individuals without the condition. These studies were systematically identified and evaluated for inclusion. Only studies published in Chinese or English were considered for inclusion in the present study. Both free text and (Mesh) keywords were utilized, including: 'von Willebrand Factor', 'von Willebrand protein', 'VWF', 'neoplasm', 'tumor', 'cancer', 'cancerization', 'cysts', 'cancerous' and 'neurofibromas'. To identify additional potentially relevant research, the citation lists of notable reviews and studies were manually searched.

Study selection. The titles, summaries and whole texts of the chosen studies were checked by two independent reviewers. If authors had published multiple works using the same sample data from the same institution, only the most recent or most comprehensive work was included. The inclusion criteria were as follows: i) All patients with cancer were diagnosed using the gold standard test of histological examination; and ii) case-control studies that included patients with and without cancer. Case reports, reviews, abstracts from conferences, letters and comments were excluded, as were studies using cells or animals, studies without access to data, duplicate papers and studies using healthy volunteers as controls.

Data extraction. Using a standardized form, two reviewers independently retrieved data from the included studies. Several key details from each study were systematically collected, including the surname of the first author, year of publication, demographics and geographical location of the study population, and ethnicities of the participants. In addition, the mean plus standard mean difference (SMD) or standard error of the mean of plasma VWF concentrations were recorded, along with the units used for VWF measurements. Any disparities between the two reviewers were addressed through discussion or, when deemed essential, by soliciting the perspective of a third reviewer.

Quality assessment. The methodological quality of each included non-randomized and observational study was independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS). This scale was used to evaluate various aspects of the design and execution of each study. Studies achieving a score of ≥7 were classified as high quality, those with a score of 6 were deemed to be medium quality, whereas those with a score of ≤5 were deemed low quality.

Statistical analysis. RevMan software (version 5.4; The Cochrane Collaboration; https://community.cochrane.org/) was utilized to calculate a pooled SMD and 95% confidence interval (CI) using a random-effects model. This approach was chosen as the included studies used a variety of measurement units. By employing SMD and 95% CI, the results were standardized across different units, such as %, IU/Dl, IU/l and IU/ml, facilitating a more coherent and meaningful comparison of the pooled effects. $P<0.05$ was considered to indicate a statistically significant result. Using the inverse-variance approach, the studies were weighted, with higher weights assigned to studies with larger sample sizes. Ethnicity-specific subgroup analyses were also performed. A Begg's funnel plot was constructed to compare and assess publication bias among the studies.

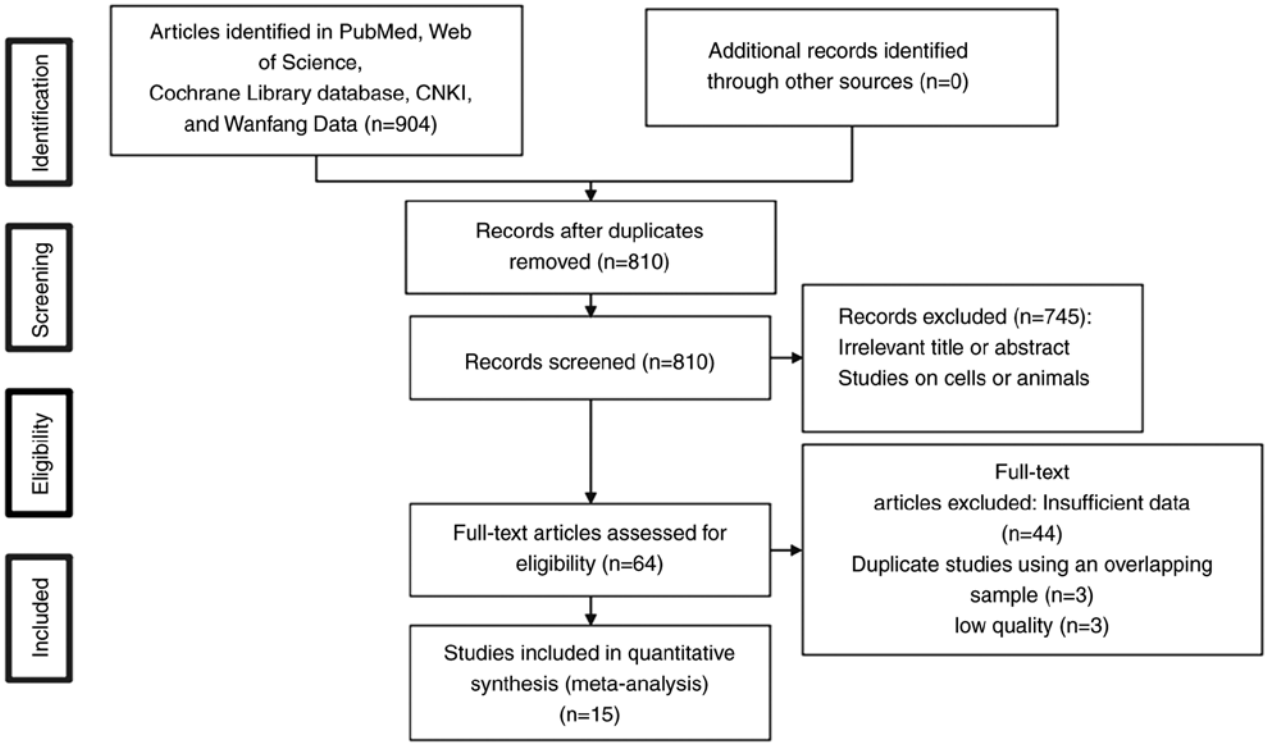

Figure 1. Flow diagram of study selection. CNKI, China National Knowledge Infrastructure.

Results

Study characteristics. Fig. 1 shows the study selection procedure. A total of 15 studies encompassing 1,403 individuals were included in the present meta-analysis (27-30,33,35-44). Table I provides a summary of the characteristics of the studies, all of which were published between 1987 and 2022. Of the included studies, four focused on breast cancer (27,41,42,44), three on colorectal cancer (29,30,37), two on prostate cancer (28,35), two on mixed cancer (39,40), two on leukemia (acute lymphoblastic leukemia and chronic myeloid leukemia) (33,36), one on non-small cell lung cancer (38) and one on bladder cancer (43). All included studies that assessed VWF expression in cancer tissues were deemed to be of high quality based to their NOS scores (*vide infra*).

Association between the VWF expression level in cancer and health. A cumulative meta-analysis was conducted on the selected studies to understand how VWF affects patients with cancer and healthy individuals. The results indicated a differential expression of VWF between individuals diagnosed with cancer and their healthy counterparts, based on an analysis of all 15 studies and 1,403 participants (SMD, 0.98; 95% CI, 0.59-1.36; Fig. 2). Since significant heterogeneity was detected (I^2=89%; P<0.00001), the random-effects model was used. The expression of VWF in different types of tumors may be the reason for this heterogeneity.

Association between the VWF expression level and metastasis. VWF expression and metastasis were found to exhibit a significant association (SMD, 0.69; 95%CI, 0.33-1.06; P=0.0002; Fig. 3). Additionally, the results revealed a notable difference in the occurrence of metastatic cancer between the two groups, with a higher VWF expression level in patients with cancer indicating a higher risk of developing metastatic disease.

Sensitivity analysis. A sensitivity analysis was conducted by sequentially excluding each study to assess its impact on the overall results. Across all studies, no significant impact was observed on the pooled outcomes, underscoring the strength and reliability of the results of the meta-analysis.

Quality evaluation. The quality of the included studies was assessed using the NOS and the results revealed that 13 studies were of high quality and 2 were of medium quality (Table II) (27-30,33,35-44). The average rating assigned to the 15 studies was 7.4. The quality of a further three studies was low (score of 5), so they were eliminated from the meta-analysis (18,45,46).

Subgroup analysis. In a study by Conlan *et al* (47), VWF levels were found to be higher in black individuals than in white individuals, indicating that there are ethnic differences in VWF levels. In a subgroup analysis categorized by ethnicity (Chinese vs. non-Chinese), plasma VWF levels were higher in patients with cancer compared with healthy individuals in both subgroups (Chinese: SMD, 1.46; -0.06-2.97; non-Chinese: SMD, 0.92; 1.48-0.35; Fig. 4).

Publication bias. Begg's funnel plots were constructed to evaluate publication bias. The almost symmetrical funnel plots showed no significant evidence of asymmetry for VWF in patients with cancer and healthy individuals (Fig. 5) or with metastatic and non-metastatic cancer (Fig. 6).

Table I. Characteristics of the studies included in the meta-analysis.

First author, year	Groups	Ethnicity	Cancer type	Sample size	Mean VWF	(Refs.)
Ablin *et al*, 1988	Healthy/cancer	Non-Chinese	Prostate	8/18	1.36±0.61/4.33±2.34 IU/ml	(35)
Athale *et al*, 2010	Healthy/cancer	Non-Chinese	Acute lympho-blastic leukemia	13/17	1.14±0.48/1.89±0.61 IU/ml	(36)
Blann *et al*, 2001	Healthy/cancer	Non-Chinese	Breast	41/41	99±20/121±29 IU/dl	(27)
Blann *et al*, 2011	Healthy/cancer	Non-Chinese	Prostate	27/31	118±26/137±20 IU/dl	(28)
Damin *et al*, 2002	Healthy/cancer metastatic	Non-Chinese	Colorectal	87/75/16	150.2±58.1/230.6±96/276±117.2 IU/dl	(37)
Dhami *et al*, 2022	Healthy/cancer	Non-Chinese	Breast	11/44	89.1±8.8/217±13 IU/dl	(44)
Gil-Bazo *et al*, 2005	Healthy/cancer/ metastatic	Non-Chinese	Colorectal	20/14/12	98.2±46.2/102.8±40.7/190±85.3 IU/dl	(30)
Guo *et al*, 2018	Healthy/cancer/ metastatic	Chinese	Non-small cell lung	102/119/64	1,019.9±789.4/1,583.5±787.7/1,812.3±675.5 IU/l	(38)
Mannucci *et al*, 2003	Healthy/cancer/ metastatic	Non-Chinese	Mixed	49/29/20	114±37/170±103/266±177%	(39)
Meschengieser *et al*, 1987	Healthy/cancer	Non-Chinese	Chronic myeloid leukemia	11/14	0.28±0.11/0.23±0.12 U/l	(33)
Pépin *et al*, 2016	Healthy/cancer	Non-Chinese	Mixed	140/20	242±158/326±158 IU/ml	(40)
Röhsig *et al*, 2001	Healthy/cancer/ metastatic	Non-Chinese	Breast	27/128/15	130.6±45/170.7±78/170.7±78 IU/dl	(41)
Wang *et al*, 2005	Healthy/cancer/ metastatic	Chinese	Colorectal	22/40/86	10.1±27/241.3±68.2/266.1±91.3%	(29)
Yigit *et al*, 2008	Healthy/cancer/ metastatic	Non-Chinese	Breast	100/100/65	78.19±43.69/99.49±47.27/105.09±48.02%	(42)
Ziętek *et al*, 1996	Healthy/cancer/ metastatic	Non-Chinese	Bladder carcinoma	35/20/31	98±42/106±51/194±41%	(43)

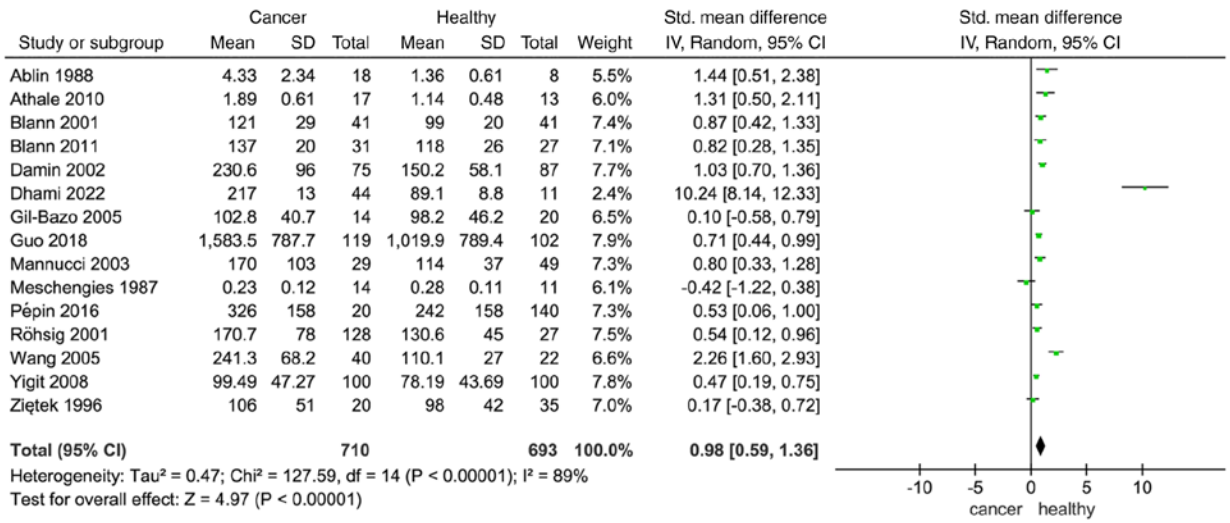

Figure 2. Forest plot illustrating the relationship between plasma von Willebrand factor levels in patients with cancer and healthy individuals. Within this graphical representation, each block corresponds to an individual study, with the size of the block reflecting its relative weight in the analysis. The horizontal line through each block represents the 95% CI for the observed effect. At the bottom of the plot, the diamond represents the pooled effect calculated across all included studies, with the width of the diamond indicating the 95% CI. CI, confidence interval; IV, inverse variance; SD, standard deviation; Std., standard.

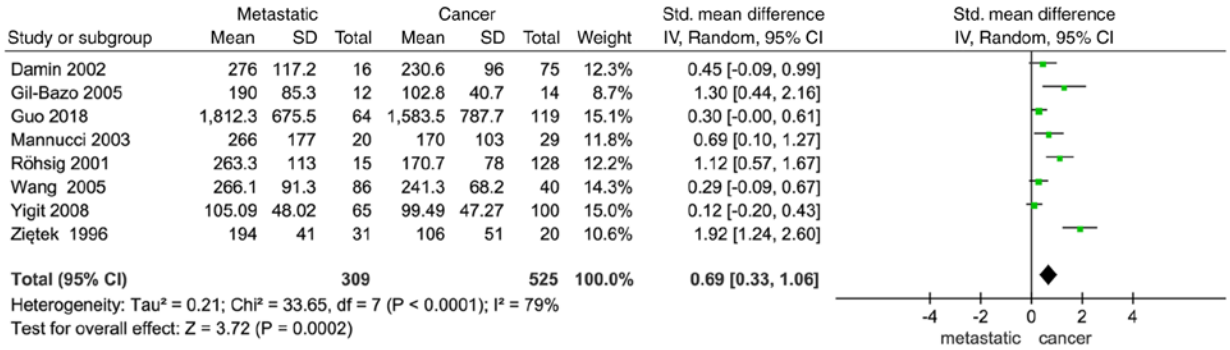

Figure 3. Forest plot illustrating the relationship between plasma von Willebrand factor levels in patients with metastatic and non-metastatic cancer. Within this graphical representation, each block corresponds to an individual study, with the size of the block reflecting its relative weight in the analysis. The horizontal line through each block represents the 95% CI for the observed effect. At the bottom of the plot, the diamond represents the pooled effect calculated across all included studies, with the width of the diamond indicating the 95% CI. CI, confidence interval; IV, inverse variance; SD, standard deviation; Std., standard.

Discussion

The present meta-analysis incorporated data from 15 studies, comprising a combined sample of comprising 710 patients with cancer and 693 healthy controls. The comprehensive analysis of SMD revealed that the plasma VWF levels of patients with cancer were significantly higher than those of healthy controls. Furthermore, patients with metastatic cancer displayed notably elevated levels of VWF compared with those with non-metastatic cancer. The results of the sensitivity analysis underscored the reliability of the combined findings. In summary, the results of the present study suggest that plasma VWF levels are a reliable indicator of a patient's predisposition to cancer development.

The clinical studies that were selected cover different types of cancer, each with its own distinct behaviors and characteristics. There may be concerns about including different types of cancer in a single meta-analysis. Including different types of cancer in a single meta-analysis may affect the final accuracy of the results. However, the decision to include multiple cancer types was based on the objective of exploring and identifying common biomarkers or therapeutic responses that might transcend specific cancer typologies. By analyzing a broader spectrum of cancers, the aim was to provide insights that could potentially apply to multiple forms of the disease, which may be particularly valuable for the development of generalized therapeutic strategies or diagnostic tools. Additionally, all analyses were carefully adjusted for cancer type as a covariate to mitigate heterogeneity and provide more accurate insights across different cancer types.

There has been a growing understanding of the association between angiogenesis and the hemostasis cascade, and their roles in the progression and spread of tumors within the bloodstream of patients afflicted by various types of cancer (48-50). Numerous patients with cancer exhibit imbalances in coagulation and fibrinolysis systems, often manifested as dysfunctions in ECs and platelets (51,52). VWF is a marker specific to ECs and an indicator of endothelial dysfunction (53,54). In addition, increased expression levels of VWF have been detected in the lung adenocarcinoma tissues of patients with cancer (55). VWF

Table II. Quality assessment of the included studies based on Newcastle-Ottawa Scale scores.

	Scores				
First author, year	Section	Comparability	Exposure	Total	(Refs.)
Ablin *et al*, 1988	3	2	3	8	(35)
Athale *et al*, 2010	3	2	3	8	(36)
Blann *et al*, 2001	4	1	2	7	(27)
Blann *et al*, 2011	3	2	3	8	(28)
Damin *et al*, 2002	2	1	3	6	(37)
Dhami 2022	3	3	3	9	(44)
Gil-Bazo *et al*, 2005	4	2	3	9	(30)
Guo *et al*, 2018	4	1	2	7	(38)
Mannucci *et al*, 2003	3	1	3	7	(39)
Meschengieser *et al*, 1987	3	2	2	7	(33)
Pépin *et al*, 2016	2	1	3	6	(40)
Röhsig *et al*, 2001	3	1	3	7	(41)
Wang *et al*, 2005	3	2	3	8	(29)
Yigit *et al*, 2008	3	1	3	7	(42)
Ziętek *et al*, 1996	2	2	3	7	(43)
John *et al*, 2020	2	1	2	5	(18)
Knöfler *et al*, 2020	2	1	2	5	(46)
Lehrer *et al*, 2019	1	1	3	5	(45)

Studies with a score of 5 were deemed poor quality and excluded from the meta-analysis.

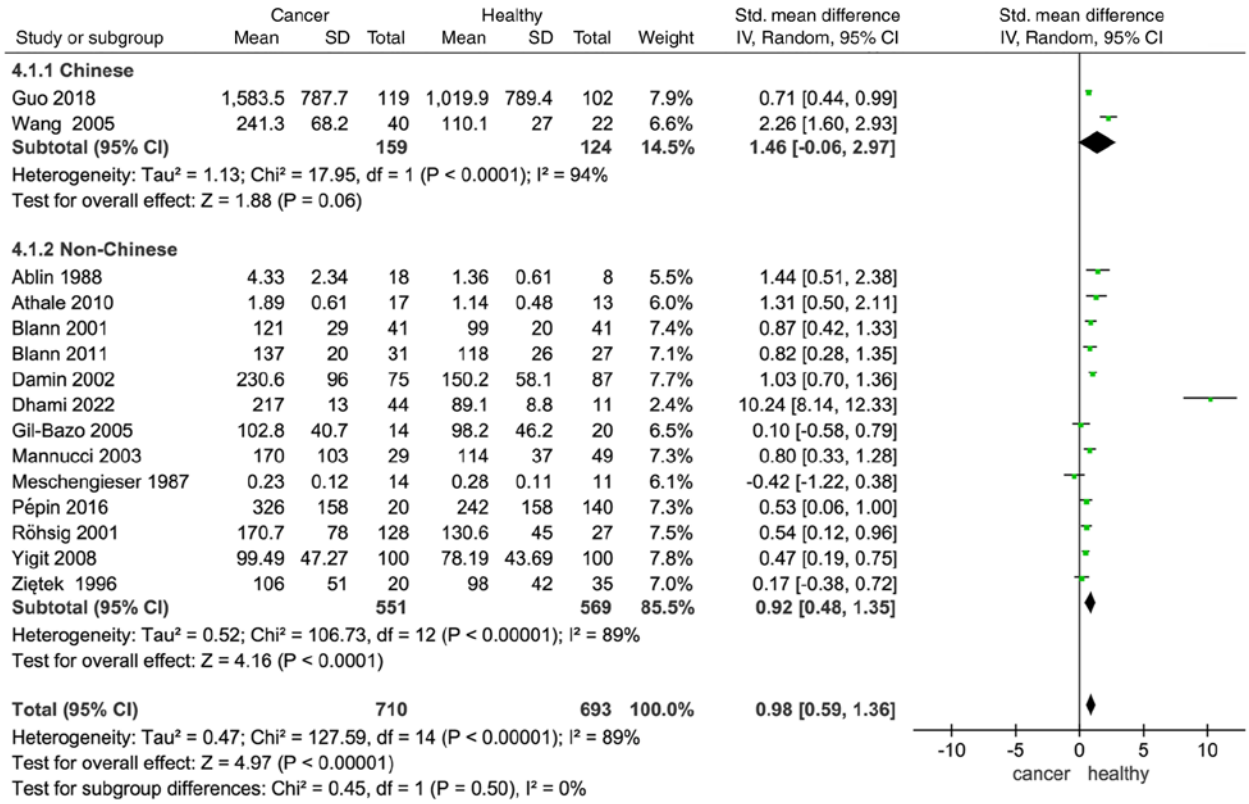

Figure 4. Forest plot displaying the relationship between plasma von Willebrand factor levels in patients with cancer and healthy individuals categorized into subgroups by ethnicity. Within this graphical representation, each block corresponds to an individual study, with the size of the block reflecting its relative weight in the analysis. The horizontal line through each block represents the 95% CI for the observed effect. At the bottom of the plot, the diamond represents the combined or pooled effect calculated across all included studies, with the width of the diamond indicating the 95% CI. CI, confidence interval; IV, inverse variance; SD, standard deviation; Std, standard.

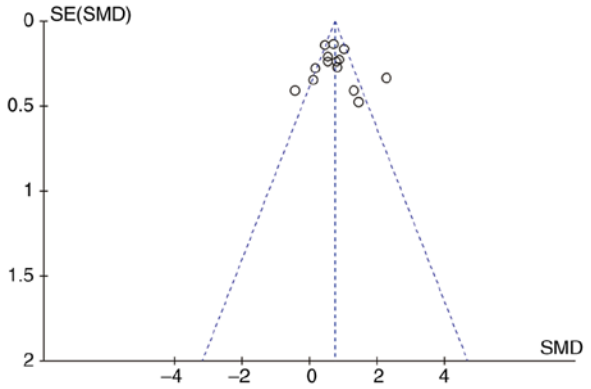

Figure 5. Funnel plot of studies comparing patients with cancer and healthy controls. SE, standard error; SMD, standard mean difference.

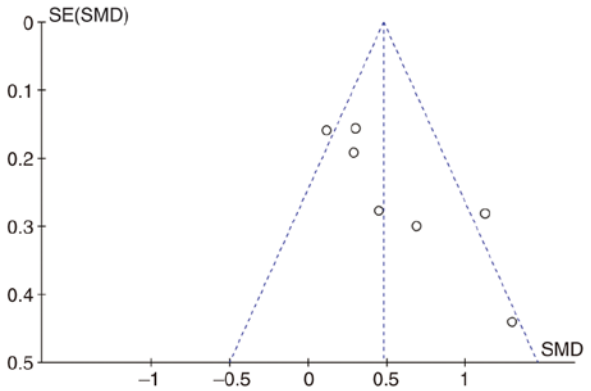

Figure 6. Funnel plot of studies comparing patients with metastatic or non-metastatic cancer. SE, standard error; SMD, standard mean difference.

is considered to mediate the binding of tumor cells to platelets, thereby facilitating their systemic dissemination (30). Previous studies have demonstrated that VWF can act as a diagnostic biomarker in a multitude of disease contexts (56-58). The results of the present study validated the association between plasma VWF levels and cancer, implying the possible diagnostic and prognostic significance of VWF in the context of cancer. Additionally, in the four studies of patients with breast cancer, it was unanimously observed that the plasma VWF levels in patients with cancer were higher compared with those in the healthy control group (27,41,42,44). In comparison with other studies, the research by Dhami *et al* (44) in 2022 appears as an outlier in the meta-analysis. The subjects included in that study were patients with metastatic breast cancer. Considering that VWF may be a potential risk factor for tumor metasatsis, the study may be an outlier as a result of the patients having a more severe illness. The weight of the study is only 2.4%, so it does not markedly impact the overall results. Furthermore, three of these studies noted that plasma VWF levels in patients with breast cancer were significantly higher in the advanced stages of disease compared with the early stages, and that this was associated with tumor staging (41,42,44). However, a study by Blann *et al* (27) found no significant differences in the plasma VWF levels among different histological types or stages of breast cancer. In the studies examining patients with colorectal cancer, plasma VWF levels were significantly higher in the patients with cancer than in the healthy individuals, and VWF was indicated to promote the distant metastasis of colorectal cancer (29,30,37).

The primary function of VWF is to initiate the blood clotting process by enabling platelets to adhere to damaged blood vessel walls in response to vascular injuries. VWF also serves as a transporter for factor VIII (59). In a study by Yigit *et al* (42), an investigation of patients with breast cancer and healthy individuals demonstrated that the patients with breast cancer exhibited elevated plasma levels of factor VIII and VWF compared with the healthy control group. VWF, secreted by ECs under the influence of thrombin, vasoactive amines and various cytokines, is an adhesive glycoprotein with the ability to effectively bind to tumor cells and platelets, potentially contributing to the formation of microthrombi. VWF also prolongs tumor cell survival by protecting the cells from immune system attacks, turbulence and frictional forces (60). The aggregation of platelets and tumor cells promotes the metastatic process by facilitating the adhesion of tumor cells and their subsequent migration through vascular walls (61). In addition, cadmium, a well-known carcinogen, increases VWF expression and secretion in ECs (62,63).

Metastasis entails a cascade of events, including modifications in cellular interactions, the formation of new blood vessels, degradation of the extracellular matrix, evasion of immune surveillance and adhesion to the surrounding matrix (64). The interactions of tumor cells with the sub-endothelial matrix are crucial for metastasis. The tumor cells release thrombin, which induces the production of VWF in ECs and thereby promotes tumor cell adhesion (65,66). The glycoproteins GPIb and GPIIb/IIIa expressed by tumor cells (67) may facilitate tumor cell-platelet binding by interaction with plasma VWF, thus promoting the metastasis process. Furthermore, this interaction leads to heterotypic cell aggregation, which reduces the recognition of tumor cells by the immune system and increases their ability to bind to the lining of blood vessels, such that it surpasses that of individual tumor cells (68).

In summary, the present meta-analysis involved the synthesis of data concerning plasma VWF levels in individuals with and without cancer, with a focus on comparing the observed variances. Each study included in the meta-analysis underwent evaluation using the NOS. However, certain limitations should be acknowledged. First, the number of studies eligible for the meta-analysis was comparatively limited. Second, the studies employed varied methodologies and measurement units for the plasma VWF levels, introducing potential inconsistencies. Third, while prior research indicates an association between blood type and VWF levels (55,58), the absence of specific blood type data in the included studies precluded a detailed subgroup analysis in this context. Additionally, due to the current research on VWF being conducted predominantly at the cellular and animal level, clinical cases concerning the expression of VWF in tumors are extremely limited.

In conclusion, the results of the present meta-analysis revealed that individuals with cancer demonstrated significantly upregulated plasma VWF levels compared with healthy individuals. Furthermore, plasma VWF levels were significantly elevated in patients with metastatic cancer compared with patients with non-metastatic cancer. These findings suggest that VWF may serve as a promising biomarker for the diagnosis of cancer.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

JL and LQ contributed to the design and conceptualization of the study. XW, XZ and CZ collected and analyzed the data. XW wrote the original draft of the text, while the other contributors provided feedback on earlier drafts. All authors read and approved the final version of the manuscript. XW, XZ and CZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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