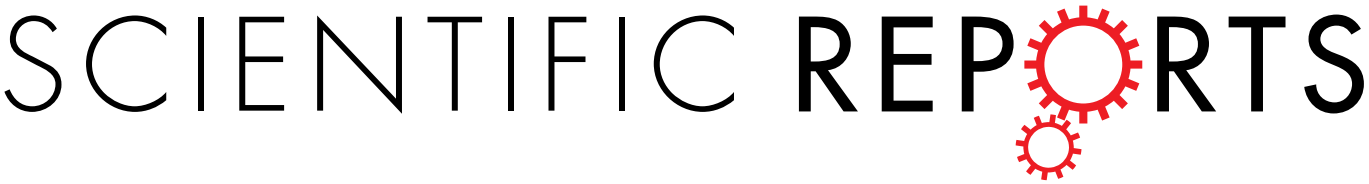

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The effects of lung and prostate cancer bone metastasis on serum osteoprotegerin levels: a meta-analysis

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Bone metastasis leads to skeletal-related events in final-stage cancer patients. The incidence of prostate and lung cancers increases yearly; these cancers readily invade the bone. Some recent studies have found that serum osteoprotegerin (OPG) levels may be altered in patients with bone metastasis, whereas other reports have produced inconsistent findings. Hence, we conducted a meta-analysis to examine the effects of lung and prostate cancer on serum OPG levels. A systematic literature search was conducted using PubMed, Medline, and CNKI to identify relevant studies. A total of 11 studies were included. The standardized mean difference (SMD) and 95% confidence interval (95% CI) of the bone metastasis (BM) group, the non-bone metastasis (BM-) group and healthy controls were calculated. In prostate cancer, serum OPG levels in the BM group were higher than in the BM- group and healthy controls. Additionally, no significant difference in serum OPG levels was found between the BM- group and healthy controls. In lung cancer, serum OPG levels in the BM and BM- groups were significantly increased compared with healthy controls. However, no significant difference in serum OPG levels was found between the BM and BM- groups. Studies with larger sample sizes are required to confirm these findings.

Bone metastases are often clinically manifested by patients with advanced malignant tumours and are most common in prostate and lung cancer patients[1]. In advanced lung cancer, metastatic deposits in bone are common and represent a source of pain and morbidity[2]. It is estimated that more than 35% of patients with advanced lung cancer manifest bone metastases, and a higher proportion was found in an autopsy series[3]. Similarly, as the second leading cause of cancer-related deaths in men, prostate cancer (PCa) has the ability to easily invade the bone, and more than 80% of PCa patients die from the development of bone metastasis[4,5].

Bone metastasis incites bony destruction and skeletal-related events (SREs), such as ostealgia, pathological fracture and hypercalcaemia[6]. Among patients with bone metastasis, 45%–75% experience more pain due to secondary changes of bone metastasis[7]. Furthermore, bone metastasis results in a shorter survival time and worse prognosis[8]. Hence, the early detection of bone metastasis is critical for the clinical management and accurate staging of tumours[9]. However, only a fraction of bone metastasis cases are clinically diagnosed[10].

Currently, the detection of bone metastasis mainly depends on pathology, imaging technologies and bone scans. However, most patients cannot tolerate undergoing a biopsy due to the invasiveness of the procedure. Each type of imaging technology has its own limitations: X-ray has hysteresis; CT has intense radiation; and MRI or PET/CT has a low incremental cost-effectiveness ratio. Although high-sensitivity bone scanning is widely used, the accuracy of its results is controversial due to low specificity. Hence, finding an effective and convenient detection method to diagnose bone metastasis is necessary.

It would be exciting to find a blood index that could accurately reflect bone metastasis. Recently, several new biomarkers of bone metabolism have been identified that can reflect bone turnover at an early stage. Some markers are already being widely applied in clinical practice[11]. However, the application of these biomarkers in the clinical diagnosis of bone metastases is not feasible[10]. Osteoprotegerin (OPG), also referred to as osteoclastogenesis inhibitory factor (OCIF), is a secreted glycoprotein that can suppress the function of osteoclasts (OCs); it was first observed in 1997[12]. As a soluble tumour necrosis factor receptor, OPG has become a research hotspot in many

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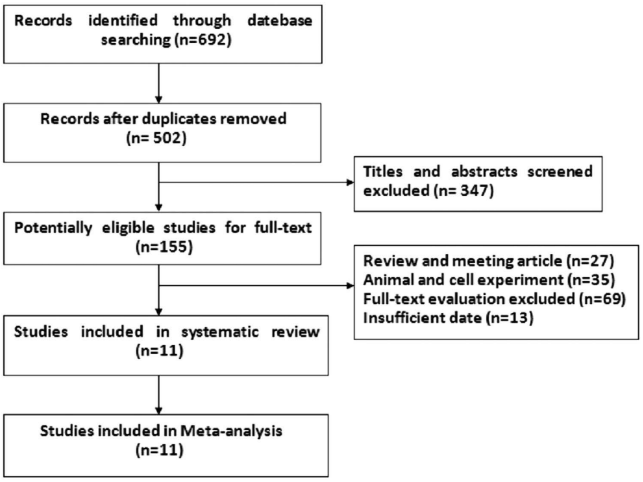

Figure 1. Flow chart of the studies identified, included and excluded.

fields, including bone metabolism. In the same year, RANKL (receptor activator of nuclear factor-κB ligand), a ligand of OPG, was discovered[13]. RANK, the exclusive receptor for RANKL, is found in OCs. In bone metabolism, as a functional spindle[12], OPG/RANK/RANKL regulates cell maturation and differentiation. Many studies have shown that lung and prostate cancer bone metastases can increase serum OPG levels. However, other studies have shown contradictory results. Hence, we conducted this meta-analysis of relevant studies to assess the effects of lung and prostate cancer bone metastasis on serum OPG levels.

Methods

Literature Search Strategy. An electronic literature search was executed in PubMed, Medline and CNKI (China National Knowledge Infrastructure, a widely used search engine in China) to identify relevant studies published up to June 2015. The following keywords or phrases were used: "OPG", "osteoprotegerin", "osteoclastogenesis inhibitory factor" and "OCIF" in combination with "(lung cancer) or (prostate cancer) bone metastasis". We manually screened the reference lists of all eligible articles to obtain more studies.

Inclusion Criteria. The inclusion criteria were as follows: 1. reports in English or Chinese; 2. cases of either primary malignancy or bone metastasis with definitive diagnoses and the collection of blood samples before the study subjects received any treatment measures; 3. the use of healthy or non-bone metastasis patients as controls; and 4. available data were supplied or obtainable through calculations.

Exclusion Criteria. Studies were excluded if they met the following criteria: 1. the absence of a case-control design; 2. review articles, case reports or conference articles; 3. animal or *in vitro* studies; 4. research involving bone primary tumours; and 5. research involving special populations (e.g., infants or pregnant women).

Study Selection. Initially, we reviewed the titles and abstracts to identify potential studies that fulfilled the inclusion criteria. In cases of uncertainty regarding the relevance of a report, a subsequent full-text assessment was conducted. Because the data used for this study were retrieved from published literature, we did not need to obtain approval from an ethics committee.

Data Extraction. Two authors independently extracted the following information: author, publication year, nationality, mean age, sample size, and serum OPG levels (mean ± SD).

Validity Assessment. Based on the primary criteria for non-randomized and observational studies of the Newcastle-Ottawa Quality Assessment scale (NOS) for meta-analyses[14], two authors completed the quality assessment. Disagreements were resolved by discussion.

Statistical Analysis. The analysis was performed with Stata 12.0 and Review Manager 5.2 software. Standard mean differences (SMDs) and the corresponding 95% confidence intervals (CIs) were used to measure serum OPG levels. Homogeneity testing was performed using the I^2 statistic. In the absence of heterogeneity ($I^2 \leq 50\%$), a fixed-effects model was used to combine the SMDs. In the opposite case, a random-effects model was used. Additionally, we performed a sensitivity analysis to assess the effect of a single study on the overall estimate by rejecting each study one at a time. Furthermore, publication bias was detected using Begg's and Egger's tests. p-values less than 0.05 were considered statistically significant.

Results

Study screening process. We initially identified 692 potential studies from the above databases. Most were excluded because they were not case-control studies or had incomplete data. Finally, 11 studies (PCa, 6; lung cancer, 5) were included[15–25] (Fig. 1). These 11 eligible studies involved 448 cases of BM (PCa, 213; lung cancer,

Author	Year	Country	Mean age*	Sample Size*
Chen *et al.*	2007	China	68/70/48	30/36/30
Roato *et al.*	2008	Italy	67/64/60	9/37/20
Zhao *et al.*	2010	China	N/N/N	27/13/N
Kamiya *et al.*	2011	Japan	69.2/66.2/62.9	51/101/49
Bu	2013	China	65.2/63.8/43.5	35/30/65
Tan	2014	China	45.5/45.8/N	61/53/N

Table 1. The characteristics of included 6 prostate cancer bone metastasis studies. Note: *: Bone metastasis group/non-bone metastasis group/healthy controls.

Author	Year	Country	Mean age*	Sample Size*
Terpos *et al.*	2009	Greece	66.6/69.6/65.3	51/28/29
Yin *et al.*	2009	China	N/N/53	40/44/65
Karapanagiotou.et al.	2010	Greece	59.6/64.3/54.8	22/18/29
Zhu *et al.*	2013	China	N/N/66	18/22/32
Li *et al.*	2013	China	N/N/N	104/82/30

Table 2. The characteristics of included 5 lung cancer bone metastasis studies. Note: *: Bone metastasis group/non-bone metastasis group/healthy controls.

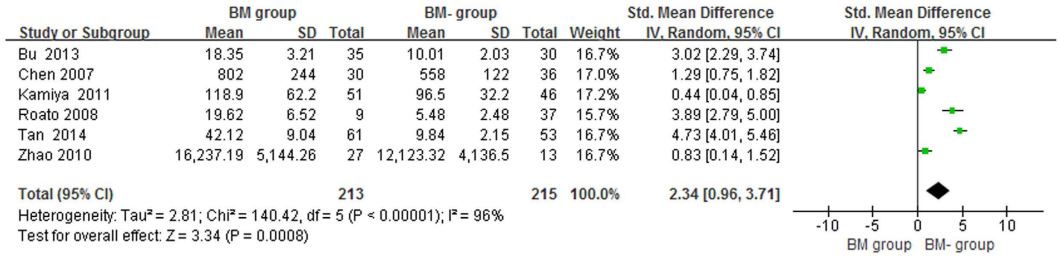

Figure 2. Forest plot for the comparison of serum OPG levels between BM group and BM- group in prostate cancer.

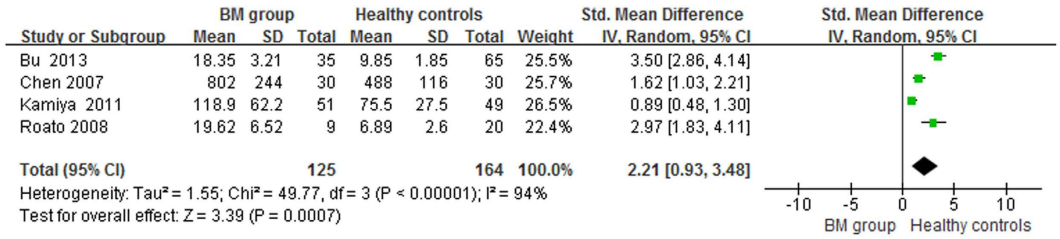

Figure 3. Forest plot for the comparison of serum OPG levels between BM group and healthy controls in prostate cancer.

235), 409 BM- (PCa, 215; lung cancer, 194) and 349 healthy controls. The general data from the 11 studies are summarised in Table 1 and Table 2.

The effect of prostate cancer bone metastasis on serum OPG levels. The pooled data suggested that the serum OPG levels in the BM group were significantly higher than in the BM- group and healthy controls, with pooled SMDs (95% CIs) of 2.34 (0.96, 3.71) and 2.21 (0.93, 3.48), $p < 0.05$, respectively (Figs 2 and 3). However, no significant difference in serum OPG levels was found between the BM- group and healthy controls (SMD = 0.22, 95% CI = −0.30 to 0.74, $p = 0.41$, >0.05; Fig. 4).

We conducted a sensitivity analysis regarding the comparison of serum OPG levels between the BM and BM- groups by sequentially eliminating one study from the relevant data; Stata 12.0 software was used to pool the SMD for the remaining studies. The results consistently suggested that no single study significantly altered the combined results (Fig. 5). Egger's regression test indicated little evidence of publication bias ($p > 0.05$).

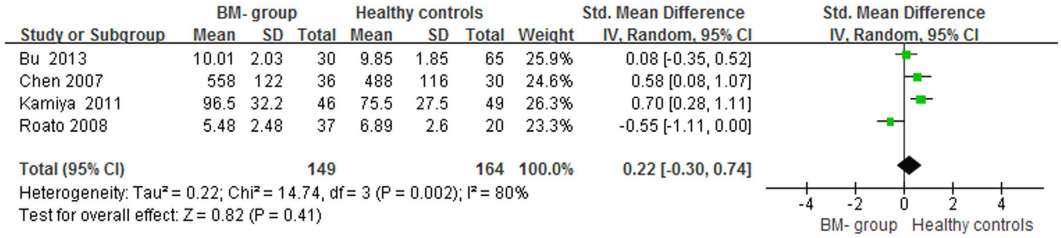

Figure 4. Forest plot for the comparison of serum OPG levels between BM- group and healthy controls in prostate cancer.

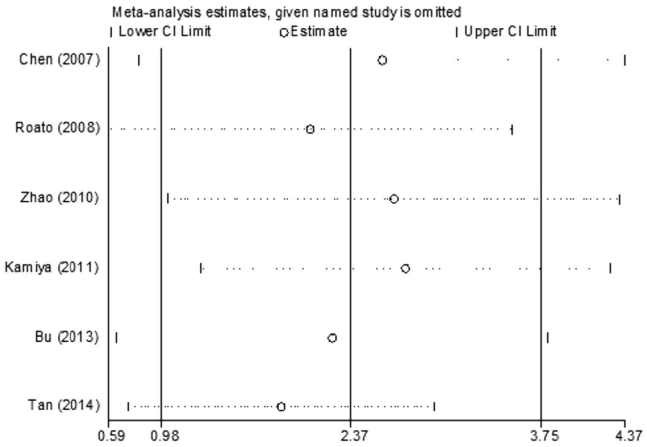

Figure 5. The plot of sensitivity analysis for the comparison of serum OPG levels between BM group and BM- group in prostate cancer.

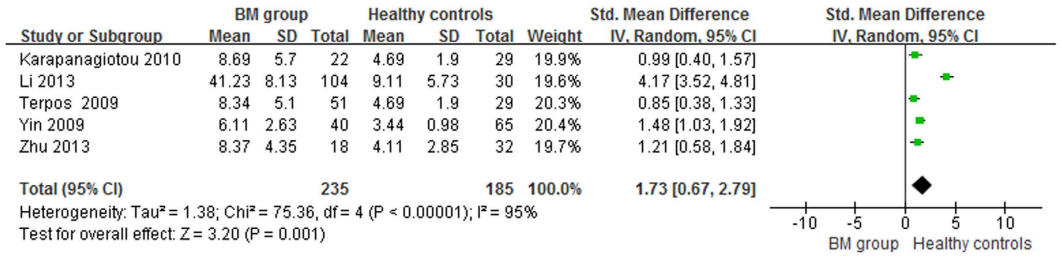

Figure 6. Forest plot for the comparison of serum OPG levels between BM group and healthy controls in lung cancer.

The effect of lung cancer bone metastasis on serum OPG levels. The lung cancer results were different from the prostate cancer results: compared with healthy controls, the serum OPG levels in the BM and BM- groups were significantly higher ($p < 0.05$), with pooled SMDs (95% CIs) of 1.73 (0.67, 2.79) and 0.80 (0.31, 1.28), respectively (Figs 6 and 7). However, no significant difference was found in serum OPG levels between the BM and BM- groups (SMD = 1.23; 95% CI = −0.40 to 2.87; $p = 0.14$, >0.05; Fig. 8).

We used Stata 12.0 software to perform the sensitivity analysis. No single study changed the combined results significantly, which indicated that the results were statistically stable and reliable (Figs 9,10 and 11). Egger's regression test indicated little evidence of publication bias ($p > 0.05$).

Discussion

Metastasis represents a major cause of mortality in cancer patients, and bone invasion is often described. Generally, lung and prostate cancers exhibit high levels of bone tropism[2,26]. To explain the cancer metastasis phenomenon, Stephen Paget proposed the "seed and soil" hypothesis in 1889, which suggests that the interplay between the properties of cancer cells and the particular organ microenvironment determines the selective growth advantage of cells[27]. Recently, most emerging evidence emphasises the crucial role of feedback interactions between tumour cells and the bone microenvironment, which lead to the establishment of a vicious cycle that acts by upregulating the physiological mechanisms that normally favour bone resorption.

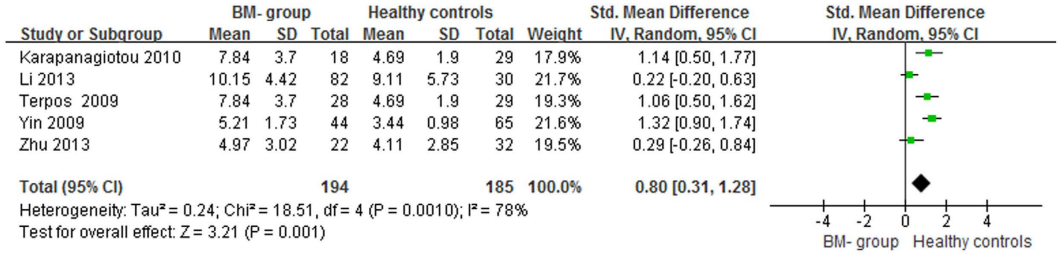

Figure 7. Forest plot for the comparison of serum OPG levels between BM- group and healthy controls in lung cancer.

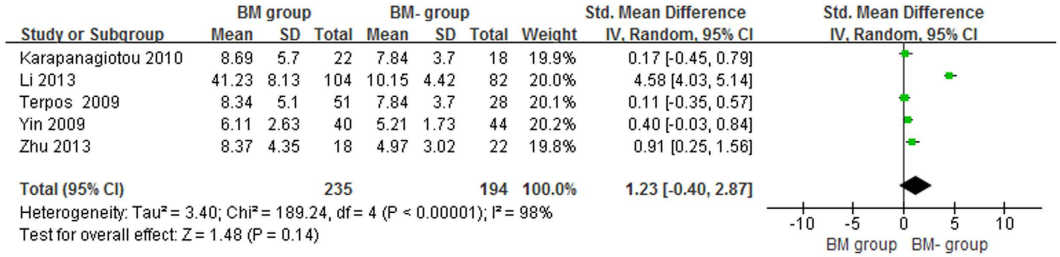

Figure 8. Forest plot for the comparison of serum OPG levels between BM group and BM- group in lung cancer.

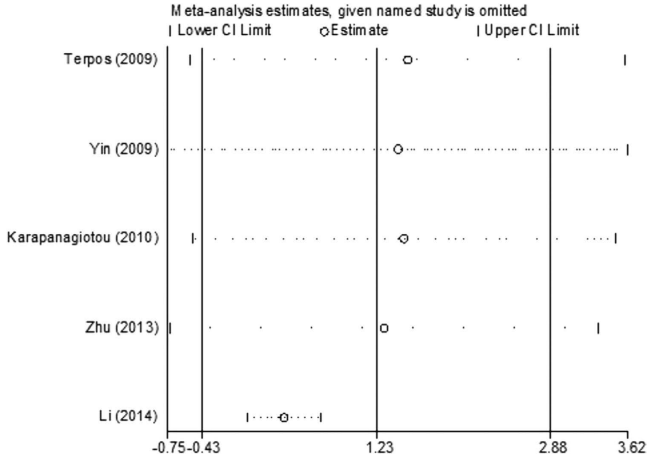

Figure 9. The plot of sensitivity analysis for the comparison of serum OPG levels between BM group and BM- group in lung cancer.

Although the osteoclasia caused by bone metastases is divided into osteolytic and osteoblastic types, mixed lesions are often described. Much evidence has shown that both resorption and formation are activated in most bone metastases; therefore, both osteolytic and osteoblastic characteristics can be observed[2]. Osteolytic and osteoblastic metastases are only the two extremes, however. The characteristics of a lesion are mainly based on the balance between resorption and formation in the bone environment. Activation and dysregulation exist in most osseous lesions, resulting in an unbalanced bone remodelling process and reflected in the complex phenotypic outcome[28–30].

OCs and osteoblasts play an important role in maintaining the balance of bone remodelling. Osteolytic metastases are thought to be caused by factors secreted by tumour cells, which activate OCs[30]. Osteoblastic metastases are believed to be caused by osteoblasts producing factors that stimulate osteoblast proliferation, differentiation and, therefore, bone formation.

Many researchers have reported that tumour cells mainly express RANKL when they adhere to the bone microenvironment[31,32]. In general, RANKL can bind to RANK to trigger signal transduction and thus promote the differentiation and maturity of OC precursors. OPG acts in this case as a "decoy" receptor of RANKL and could be considered a "protector" of bone[33]. As a paracrine regulator of OC formation, OPG was found to have an essential physiological role: OPG is produced by osteoblasts and binds to RANKL, and its constitutive production is necessary to limit the OC formation resulting from RANKL stimulation[34].

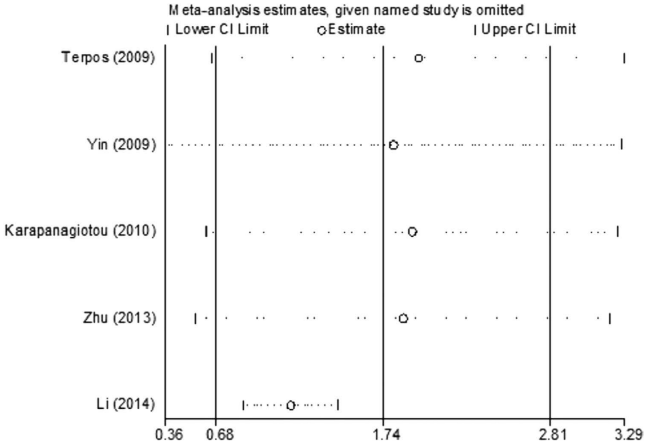

Figure 10. The plot of sensitivity analysis for the comparison of serum OPG levels between BM group and healthy controls in lung cancer.

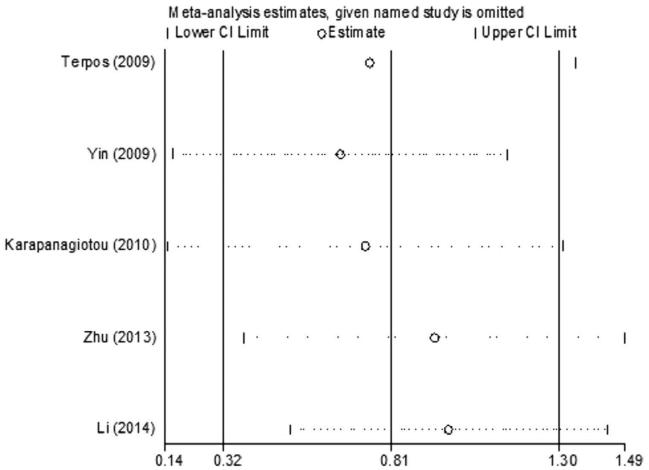

Figure 11. The plot of sensitivity analysis for the comparison of serum OPG levels between BM- group and healthy controls in lung cancer.

The RANK/RANKL/OPG system has recently been recognised as the ultimate mediator of osteoclastogenesis[30,35], and the dysregulation of the OPG–RANKL system is thought to be crucial to the bone disease connected with cancers such as prostate cancer[36]. Some studies have reported that the ratio of RANKL/OPG was increased in neoplastic disease patients with severe osteolysis, which has also been observed in multiple myeloma patients[37,38]. Recently, some studies showed that a therapy that disrupts the vicious cycle in the bone microenvironment by binding to RANKL and inhibiting its function could achieve satisfactory results. Denosumab is a fully humanised monoclonal antibody against RANKL for the prevention of SREs in patients with tumours that metastasize to bone[39]. Unlike denosumab, zoledronic acid (ZA) can prevent the prenylation of the small GTPase proteins that are essential for OC function and survival[40,41]. In 2013, Sun found that denosumab was superior to ZA in preventing complications in patients with bone metastases[42]. One year later, Henry reported that denosumab was more effective than ZA at either delaying SREs in solid bone tumours or preventing pain progression[43]. These results suggest that the RANK/RANKL/OPG system plays a key role in the process of bone metastasis from the perspective of treatment; thus, serum OPG levels could be altered in bone metastasis patients.

In our study, the pooled data on PCa bone metastasis revealed that, compared with the BM- group and healthy controls, the BM group had higher serum OPG levels. However, no difference was found between the BM- group and healthy controls. The results suggest that bone metastasis increases serum OPG levels in prostate cancer patients. The specific mechanisms underlying the increase in serum OPG levels might be due to a variety of factors. The OC is a unique cell capable of dissolving bone tissue, which plays an important role in bone remodelling. It has been shown that OPG can be secreted to inhibit osteoclastogenesis and OC survival, thus preventing the establishment of tumour lesions in bone[44–46]. *In vitro* studies have shown that some tumour cells did not express RANKL mRNA when cultured alone. However, the co-culture of these cancer cells with osteoblastic cells or bone marrow stromal cells could induce RANKL expression. This interaction between stromal cells and tumour cells is critical for metastasis[29,47]. OPG can be released to upset the interaction between OCs and stromal cells[48], which

inhibits RANKL expression by tumour cells. Despite the potential of OPG in inhibiting OC activation, it also binds to TNF-related apoptosis-inducing ligand (TRAIL), making tumour cells resistant to apoptosis. It was shown that prostate cancer and bone marrow stromal cells could express OPG to enhance tumour cell survival by inhibiting TRAIL[36,49,50]. OPG can prevent the association between TRAIL and its death-inducing receptor, thereby increasing the survival of tumour cells that have metastasised to the bone microenvironment[29,51,52]; this may be one reason that OPG levels increase when tumours metastasise to bone.

However, we found that bone metastasis embodied a different phenomenon in lung cancer. Compared with healthy controls, the BM and BM- groups had higher serum OPG levels. No difference was found between the BM group and the BM- group. Serum OPG levels are increased in lung cancer regardless of whether it is complicated by bone metastases. The literature on the role of OPG and its involvement in metastatic bone disease is somewhat contradictory. This may suggest that OPG is not associated with skeletal metastasis at all, but rather with the tumour load per se[17]. In addition, preclinical data suggest that OPG plays a role in promoting angiogenesis[53], which may be a less important reason for OPG expression in lung cancer bone metastasis.

The meta-analysis revealed that serum OPG levels could reflect prostate cancer bone metastasis. This has a certain clinical utility in that abnormally elevated serum OPG levels in prostate cancer patients may be associated with bone metastases. Serum OPG measurements can be used to supplement various existing diagnostic methods to increase the precision and convenience of bone metastasis diagnosis. However, we found that OPG was not associated with lung cancer bone metastasis, but rather with the presence of the tumour. This finding perhaps hints that not all bone metastases can be detected by measuring serum OPG. Recently, a study of bone metastasis treatment showed that clinical efficacy was consistent with the relative reduction observed in bone turnover markers[43]. This may suggest that OPG could be used as an indicator to evaluate the clinical efficacy of treatment.

We should note some limitations of our study: 1. the included studies were based on a case-control design, in which selection bias was inevitable; 2. the sample size of the included studies was relatively small, and several studies were excluded due to insufficient data; 3. we could not avoid the possibility that other unmeasured or inadequately measured factors confounded the results; and 4. our inclusion criteria might have introduced selection bias, although little statistical evidence of publication bias was observed.

Conclusion

The present meta-analysis suggests that serum OPG levels can reflect prostate cancer bone metastasis to some extent, which indicates that serum OPG measurements can be used to supplement existing diagnostic methods for bone metastasis. However, serum OPG levels may more accurately reflect the existence of lung cancer itself. Further studies on this topic with larger sample sizes are needed.

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Additional Information

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