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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Risk of high-grade bleeding in patients with cancer treated with bevacizumab: a meta-analysis of randomized controlled trials

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Abstract
Purpose High-grade bleeding is a serious adverse event associated with bevacizumab, a humanized monoclonal antibody targeting vascular endothelial growth factor and widely used in the current cancer treatments. The aim of this study was to gain a better understanding of the overall incidence and risk of high-grade bleeding in cancer patients who receive bevacizumab therapy.
Methods We performed a meta-analysis of relevant randomized controlled trials (RCTs) identified in PubMed, Cochrane library, Embase, and American Society of Clinical Oncology conferences. Overall relative risks (RRs), incidence rates, and 95% confidence intervals (CIs) were calculated using a random-effects model. The primary clinical endpoint was high-grade bleeding (grade 3 or above).
Results A total of 14,277 patients with a variety of solid tumors from 22 RCTs were included in the present analysis. The addition of bevacizumab to cancer chemotherapy significantly increased the risk of high-grade bleeding (RR 1.60, 95% CI 1.19–2.15), with RRs of high-grade bleeding among patients receiving bevacizumab at 2.5 and 5 mg/kg per week of 1.27 (95% CI 0.95–1.71) and 3.02 (95% CI 1.85-4.95), respectively. The overall incidence of high-grade bleeding among patients receiving bevacizumab was 2.8% (95% CI 2.1–3.8). Higher risks were observed in patients with non-small-cell lung cancer (RR 3.41, 95% CI 1.68–6.91), renal cell carcinoma (RR 6.37, 95% CI 1.43–28.33), and colorectal cancer (RR 9.11, 95% CI 1.70–48.79) who were receiving bevacizumab at 5 mg/kg per week.
Conclusions Among the patients included in the trials analyzed in this meta-analysis, the addition of bevacizumab to cancer chemotherapy significantly increased the risk of high-grade bleeding. The risk may be dose-dependent and may vary with tumor type.

Keywords Bevacizumab · Bleeding · Meta-analysis · Chemotherapy

Background

Angiogenesis plays a pivotal role in tumor growth, progression, and metastasis [1, 2], and the inhibition of angiogenesis has been a major focus of new cancer therapeutics. In the past several years, angiogenesis inhibitors targeting the vascular endothelial growth factor (VEGF) pathway have come under extensive investigation. Bevacizumab (Avastin; Genentech, South San Francisco, CA), a recombinant humanized monoclonal antibody against VEGF, is widely used in current cancer treatments. It is the first angiogenesis inhibitor approved as a first-line treatment for metastatic colorectal cancer in combination with fluorouracil-based and oxaliplatin-based chemotherapy [3–9]. Bevacizumab has also been approved for the treatment of advanced non-small-cell lung cancer in combination with carboplatin and paclitaxel [10]. Additionally, bevacizumab has been shown to improve progression-free survival in patients with metastatic renal cell carcinoma and metastatic breast cancer [11–15]. The efficacy of bevacizumab in many other malignancies, such as ovarian cancer and gastric cancer, is currently undergoing extensive assessment.

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As with other angiogenesis inhibitor drugs, bevacizumab is associated with substantial side-effects, such as hypertension, proteinuria, bleeding, arterial and venous thromboembolic events, and wound-healing complications [16]. High-grade bleeding associated with bevacizumab is a common side-effect observed in clinical trials and may have life-threatening consequences [4, 5, 7–15, 17–27]. However, the risk of high-grade bleeding in cancer patients receiving bevacizumab that has been reported in clinical trials has not been completely consistent, and none of these trials was large enough to define the overall risk. In addition, an individual trial may be limited to the study of one tumor type. Therefore, we propose that pooling analyses of the current studies may provide a better understanding of the overall risk of high-grade bleeding among cancer patients who receive bevacizumab. To address this issue, we carried out a systematic review of the published studies and combined the results from relevant randomized controlled trials (RCTs) for a meta-analysis.

Methods

Data sources

The study was performed using a prespecified search strategy and study eligibility criteria. We did an extensive search of PubMed (up to September 2010), Cochrane Central Register of Controlled Trials (up to Cochrane Library Issue 3, 2010), and Embase (1980 to September 2010) with the aim of identifying relevant RCTs for our meta-analysis. Abstracts and meeting presentations from the American Society of Clinical Oncology conferences held between January 2000 and September 2010 were also searched for relevant RCTs. We restricted the search to RCTs. Search term combinations were "bevacizumab", "avastin", and "cancer". The language of the research papers was not restricted. All reference lists from the relevant articles and reviews were hand searched for additional eligible studies. Experts in the field were also consulted, who subsequently confirmed the results of the search for RCTs and were unable to identify any additional eligible study. The articles that were not freely available to us were requested from the authors.

Study selection

Two reviewers (XFH and WSX) independently carried out a literature search and examined relevant RCTs for further assessment. Only those RCTs that directly compared cancer patients treated with and without bevacizumab, respectively, were selected for analysis. Phase I and single-arm phase II trials were excluded due to their lack of control groups. Specifically, clinical trials that met the following criteria were included in the meta-analysis: (1) prospective phase II and phase III RCTs in patients with cancer; (2) random assignment of participants to bevacizumab treatment or control groups in addition to concurrent chemotherapy and/or treatment with a biological agent; (3) available data, including the event or incidence of bleeding and sample size for analysis.

Qualitative assessment

Evaluation of the methodological quality of the RCTs included in the meta-analysis was performed independently by two reviewers (XFH and WSX) using the Jadad scoring system as follows [28]. One point was awarded for the presence of randomization, blinding, and data on study withdrawals, respectively. If the randomization or blinding procedures was appropriate, one point was awarded for each procedure; no points were awarded if no data were provided on the methodology of the above-mentioned procedures. Finally, if any of these procedures were not deemed appropriate, one point was deducted for each of the "inappropriate" procedures. The maximum score that could be attributed to an RCT was 5. An RCT with a score >2 was considered to be an RCT of adequately good quality [29, 30].

Data extraction

Two reviewers (XFH and WSX) independently extracted data from the trials included in the meta-analysis using a predesigned review form. In the case of any disagreement between the two reviewers, a third reviewer extracted the data, and the results were attained by consensus. We contacted the authors of trials for the missing data when necessary. Data on study characteristics (methodology, underlying malignancy of included patients, concurrent treatment, follow-up duration, number of patients, bevacizumab dose, and publication details) and clinical endpoints were extracted.

Clinical endpoint

Bleeding events in the safety profile of each trial were selected as the main clinical endpoint of our meta-analysis and recorded in the included trial according to versions 1, 2, or 3 of the Common Terminology Criteria for Adverse Events (CTCAE; http://ctep.cancer.gov). These three versions are similar in terms of their grading of bleeding, with grade 1 indicating mild bleeding (intervention not indicated), grade 2 indicating symptomatic bleeding (medical intervention indicated), grade 3 indicating the need for

transfusion, interventional radiology, or endoscopic or operative intervention (i.e., hemostasis of bleeding site), grade 4 indicating life-threatening consequences (major urgent intervention indicated), and grade 5 indicating death. We included the incidence of allgrade and high-grade bleeding (grade 3 or above) in our analysis.

Data analysis and statistical methods

We used Stata ver. 10.0 (StataCorp, College Station, TX) for all statistical analyses. The number of patients with bleeding was summarized from the data extracted on all patients assigned bevacizumab treatment in the individual trial. For each trial, the proportion of patients with bleeding was calculated and the 95% confidence interval (CI) was derived. We explored a dose–effect relationship by further dividing bvacizumab therapy into low-dose (5 or 7.5 mg/kg per dose per schedule, which is equivalent to 2.5 mg/kg per week) and high-dose (10 or 15 mg/kg per dose per schedule, which is equivalent to 5 mg/kg per week) therapy. The relative risk (RR) of bleeding in patients assigned to bevacizumab treatment was also calculated and compared only with those assigned to a control treatment in the same trial.

For the meta-analysis, we used a random-effects model applying the method of DerSimonian and Laird, which accounts for both within-study and between-study variation [31]. We assessed statistical heterogeneity among studies included in our meta-analysis with the Q statistic, and we quantified inconsistency with the I^2 statistic. We judged as invalid the assumption of heterogeneity if $p<0.1$. To investigate possible reasons for heterogeneity, we did subgroup analyses by underlying malignant disease. The publication bias was assessed by examining the funnel plot.

Results

The flow diagram (Fig. 1) shows the detailed screening and selection process that we applied before including trials in our meta-analysis. The search was performed in PubMed, the Cochrane Central Register of Controlled Trials, Embase, and the American Society of Clinical Oncology conferences. We obtained 61 full papers from 357 studies for detailed evaluation and ultimately identified 22 RCTs, including eight phase II and 14 phase III studies, which fulfilled all of the criteria for inclusion in the meta-analysis.

The main characteristics of the 22 included RCTs are presented in Table 1. Malignant diseases included were non-small-cell lung cancer (four studies), colorectal cancer (eight studies), breast cancer (three studies), renal-cell carcinoma (three studies), pancreatic carcinoma (two studies), gastric cancer (one study), and mesothelioma (one study). The total population of the included trials comprised 14,277 patients. Patients were enrolled according to prespecified eligibility criteria for each trial. The baseline Eastern Cooperative Oncology Group (ECOG) performance status for most patients was between 0 and 1. Randomized treatment allocation sequences were generated in all trials. Eight trials were double-blinded and placebo controlled [12, 15, 17, 21–25]; three other trials had placebo as controls [5, 8, 27]; the rest of the trials had active controls [4, 7, 9–11, 13, 14, 18–20, 26]. Bleeding was assessed and recorded according to the CTCAE version 1, 2, or 3 criteria. Version 1 was used in two trials [7, 18], version 2 was used in eight trials [4, 5, 9–11, 13, 19, 24], and version 3 was used in two trials [8, 15]; the remainder of the trials did not specify the CTCAE version. Follow-up time was not specified in eight trials [7, 14, 17, 20, 23, 25–27]. The quality of all the trials included in the meta-

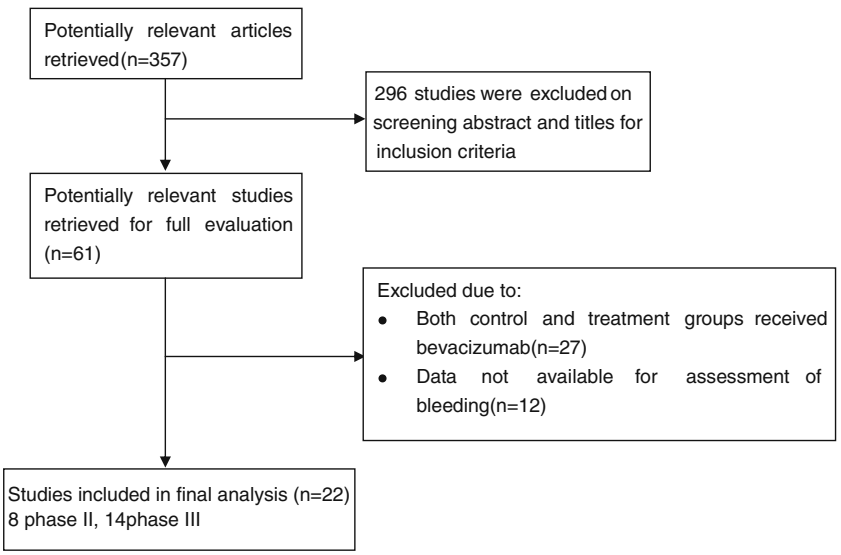

Fig. 1 Flow diagram of the randomized controlled trials reviewed

Table 1 Characteristics of randomized controlled clinical trials included in the meta-analysis

Study	Trial phase	Enrolled patients (*n*)	Number of patients for analysis	Type of underlying malignancy	Duration of follow-up (months)	Concurrent treatment	Bevacizumab dose (mg/kg per week)
Herbst et al. [19]	II	122	81	Non-small-cell lung cancer	15.8	Docetaxel or pemetrexed	5
Reck et al. [17]	III	1043	986	Non-small-cell lung cancer	NA	Cisplatin and gemcitabine	2.5 or 5
Sandler et al. [10]	III	878	867	Non-small-cell lung cancer	19.0 (NA)	Paclitaxel and carboplatin	5
Johnson et al. [18]	II	99	98	Non-small-cell lung cancer	14.7 (NA)	Carboplatin and paclitaxel	2.5 or 5
Giantono et al. [4]	III	829	572	Colorectal cancer	28.0 (NA)	Oxaliplatin, fluorouracil, and leucovorin	5
Hurwitz et al. [6]	III	813	790	Colorectal cancer	18.0 (NA)	Irinotecan, bolus fluorouracil, and leucovorin	2.5
Kabbinavar et al. [9]	II	209	204	Colorectal cancer	14.8 (NA)	Bolus fluorouracil, and leucovorin	2.5
Saltz et al. [8]	III	1401	1369	Colorectal cancer	27.6 (NA)	Oxaliplatin, fluorouracil, and 1oxaliplatin or capecitabine, and leucovorin	2.5
Allegra et al. [20]	III	2710	2647	Colorectal cancer	NA	Fluorouracil, leucovorin, and oxaliplatin	2.5
Kabbinavar et al. [7]	II	104	102	Colorectal cancer	NA	Fluorouracil /Leucovorin	2.5 or 5
Price et al. [26]	II	471	471	Colorectal cancer	NA	Capecitabine	2.5
Hambleton et al. [27]	II	83	83	Colorectal cancer	NA	irinotecan/5-FU/ leucovorin (IFL)	2.5
Miles et al. [12]	III	736	736	Metastatic breast cancer	10.2 (0–17·5)	Docetaxel	2.5 or 5
Miller et al. [11]	III	722	711	Metastatic breast cancer	25.9 (NA)	Paclitaxel	5
Miller et al. [13]	III	462	442	Metastatic breast cancer	14.8 (NA)	Capecitabine	5
Escudier et al. [15]	III	649	641	Renal cell carcinoma	13.3 (0–25.6)	Interferon α	5
Rini et al. [14]	III	732	709	Renal cell carcinoma	46.2 (range 45.2-48.2)	Interferon α	5
Yang et al. [24]	II	116	116	Renal cell carcinoma	27 (NA)	NA	2.5 or 5
Cutsem et al. [21]	III	607	583	Metastatic pancreatic cancer	6·7 (NA)	Gemcitabine and erlotinib	2.5
Kindler et al. [22]	III	602	523	Metastatic pancreatic cancer	11.3(NA)	Gemcitabine	5
Kang et al. [25]	III	774	774	Advanced gastric cancer	NA	Capecitabine and cisplatin	2.5
Karrison et al. [23]	II	115	108	Malignant mesothelioma	NA	Gemcitabine/cisplatin	5

NA Information not available

analysis was acceptable. We examined the funnel plot [standard error (SE) of log RRs plotted against RRs) to estimate publication bias and obtained a symmetric inverse funnel distribution.

In the present meta-analysis, we calculated the overall RR of high-grade bleeding associated with bevacizumab treatment compared with the control treatment. Data were available for 7136 patients who received bevacizumab and 6,310 patients who received control treatments in the 22 trials included in our meta-analysis. The risk of high-grade bleeding in controls was very low in most of the studies. The overall RR of high-grade bleeding associated with bevacizumab versus the control was 1.60 (95% CI 1.19–-2.15) (Fig. 2). We found the overall RR of all bleeding was 2.65 (95% CI 2.08–3.38).

The incidence of high-grade bleeding ranged between 0.4 and 7.7%, with the highest and lowest incidence reported in the trial performed by Herbst et al. [19] and and Miller et al. [13], respectively. Using a random-effects model, we determined that the overall incidence of high-grade bleeding in patients receiving bevacizumab was 2.8% (95% CI, 2.1–3.8%) (Fig. 3) and that the incidence of all-grade bleeding was 25% (95% CI 18–34%).

To understand further the role of bevacizumab in the pathogenesis of high-grade bleeding, we assessed whether the dose of bevacizumab is related to the risk of developing high-grade bleeding. The RR of high-grade bleeding associated with low-dose bevacizumab (2.5 mg/kg per week) was 1.27 (95% CI 0.95–1.71) as calculated from 11 RCTs (Fig. 4), while the RR for high-dose bevacizumab (5 mg/kg per week) was 3.02 (95% CI 1.85–4.95) as calculated from 11 RCTs (Fig. 5). Based on these results, it would appear that the risk of high-grade bleeding with bevacizumab treatment was dose dependent among the patients in these trials.

Patients with different tumors might be at different risks of bleeding due to differences in tumor biology and the associated treatment. We determined whether having a specific type of cancer was associated with a higher risk for high-grade bleeding relative to other cancers. As shown in Fig. 5, the risk of high-grade bleeding varied according to tumor type. Relatively high RRs for high-grade bleeding associated with high-dose bevacizumab were found among patients with non-small-cell lung cancer (RR 3.41, 95% CI 1.68– 6.91), renal cell carcinoma (RR 6.37, 95% CI 1.43–28.33), and colorectal cancer (RR 9.11, 95% CI 1.70–48.79); relatively low RRs were seen in patients with metastatic breast cancer (RR 1.33, 95% CI 0.32–5.46) and pancreatic cancer (RR 1.54, 95% CI 0.51–4.64). Similarly, the overall incidence of high-grade bleeding in patients receiving high-dose bevacizumab was 3.2% (95% CI, 2.1–4.7%), with a relatively high incidence in non-small-cell lung

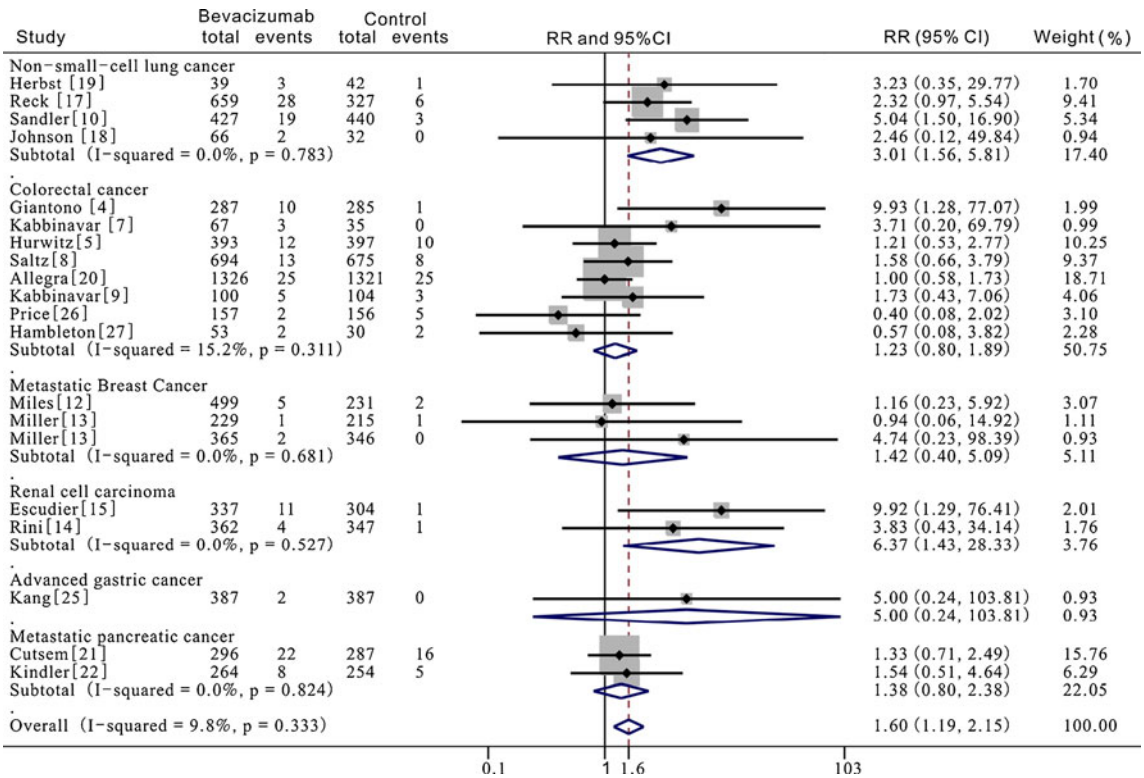

Fig. 2 Meta-analysis of relative risk (*RR*) of high-grade bleeding based on a comparison of bevacizumab and non-bevacizumab treatment for cancer. *CI* Confidence interval

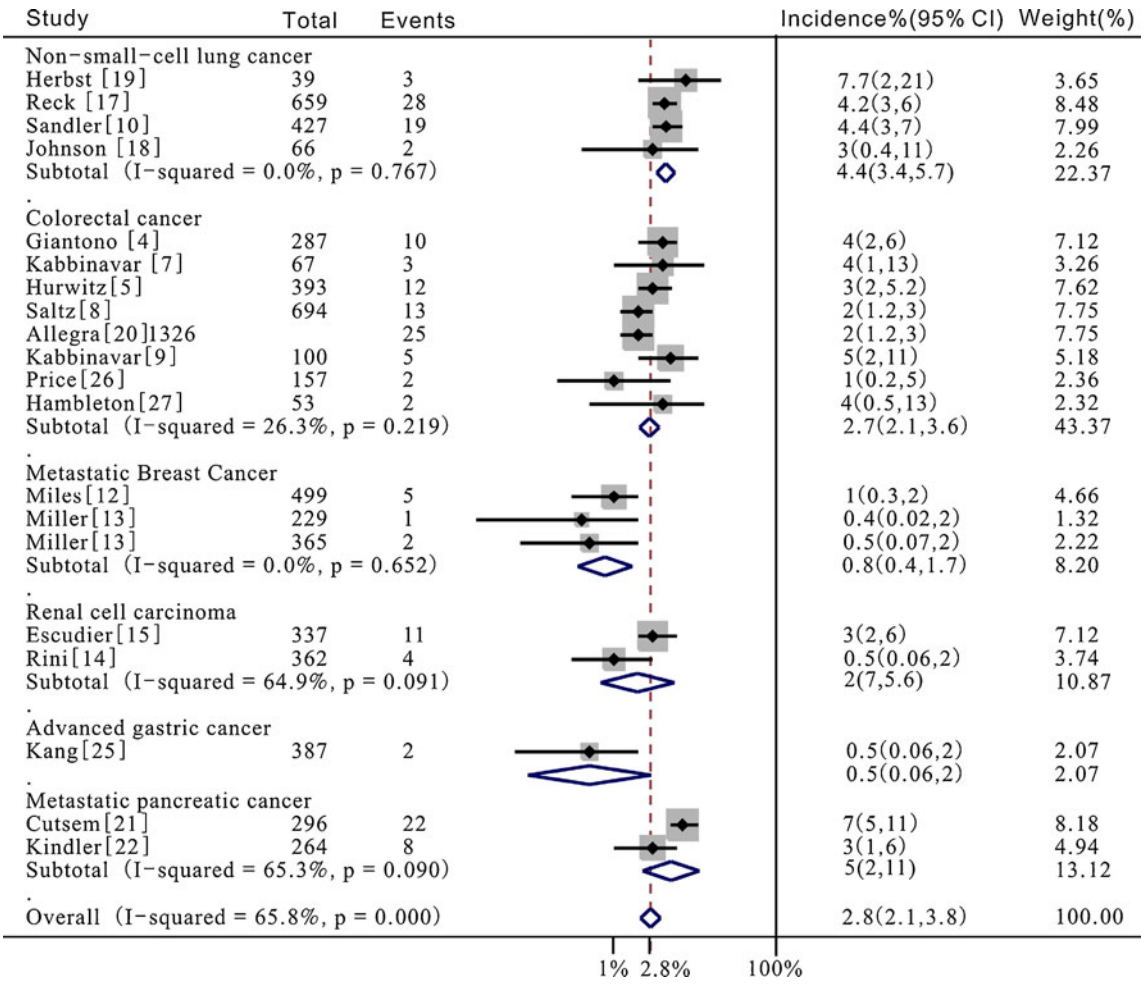

Fig. 3 Meta-analysis of incidence of high-grade bleeding in cancer patients receiving bevacizumab

cancer patients (5%, 95% CI 3.6–6.9%) and colorectal cancer patients (5.1%, 95% CI 2.2–12.2%) and a relatively low incidence in metastatic breast cancer patients (0.6%, 95% CI 0.2–1.7%)(Fig. 6). The addition of low-dose bevacizumab to cancer therapy did not significantly increase the risk of high-grade bleeding (Fig. 4), and the different type of cancer patients receiving low-dose bevacizumab therapy had a similar incidence of high-grade bleeding (data not shown).

Discussion

The study presented here is a systematic review with meta-analysis aimed at investigating the overall incidence and risk of high-grade bleeding among cancer patients who receive bevacizumab therapy. The results showed that the addition of bevacizumab to cancer therapy significantly increased the risk of high-grade bleeding, with an overall RR of 1.60 (95% CI 1.19–2.15) and incidence of 2.8% (95% CI 2.1–3.8%) among patients with a variety of solid tumors from 22 RCTs (Figs. 2, 3). In addition to bevacizumab, other angiogenesis inhibitors, such as sorafenib and sunitinib, which block the activity of VEGF receptors, are also associated with a significant increase in the risk of bleeding [32]. Based on the results of previous studies, the incidences of high-grade bleeding for sorafenib and sunitinib are 2.2 (95% CI 1.3–3.6) and 3.0% (95% CI 1.3–6.8) [32], respectively; in comparison, we found an incidence of 2.8% (95% CI 2.1–3.8%) for bevacizumab in this study. Thus, it would appear that the absolute risk of high-grade bleeding induced by these different angiogenesis inhibitors is similar.

The association of bevacizumab with bleeding may be directly related to its inhibitory effect on VEGF signaling. VEGF is important for endothelial cells to maintain the architecture and integrity of the microvasculature. When VEGF signaling is blocked by bevacizumab, the repair and renewal capacity of endothelial cells in response to trauma could be impaired, which would induce the increased risk of bleeding [33, 34]. In clinical trials, the onset of high-grade bleeding in bevacizumab-treated

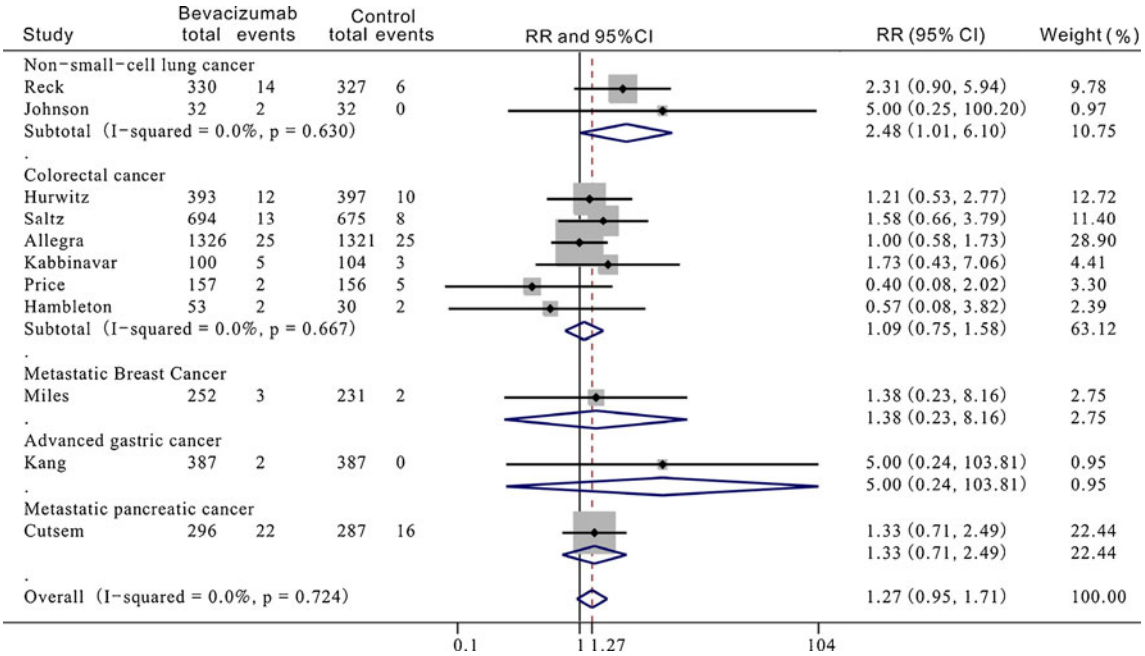

Fig. 4 Meta-analysis of RR of high-grade bleeding based on a comparison of patients receiving low doses of bevacizumab (2.5 mg/kg per week) and those receiving a non-bevacizumab treatment for cancer

patients can occur at any time during therapy. However, the risk factors for the development of high-grade bleeding, an important issue in reducing the risk of occurrence, have not been fully elucidated.

The bleeding associated with bevacizumab treatment may be attributable to known risk factors, such as age, race, sex, bevacizumab dose, and underlying cancer, or to the concurrent use of anticoagulants. We first assessed whether

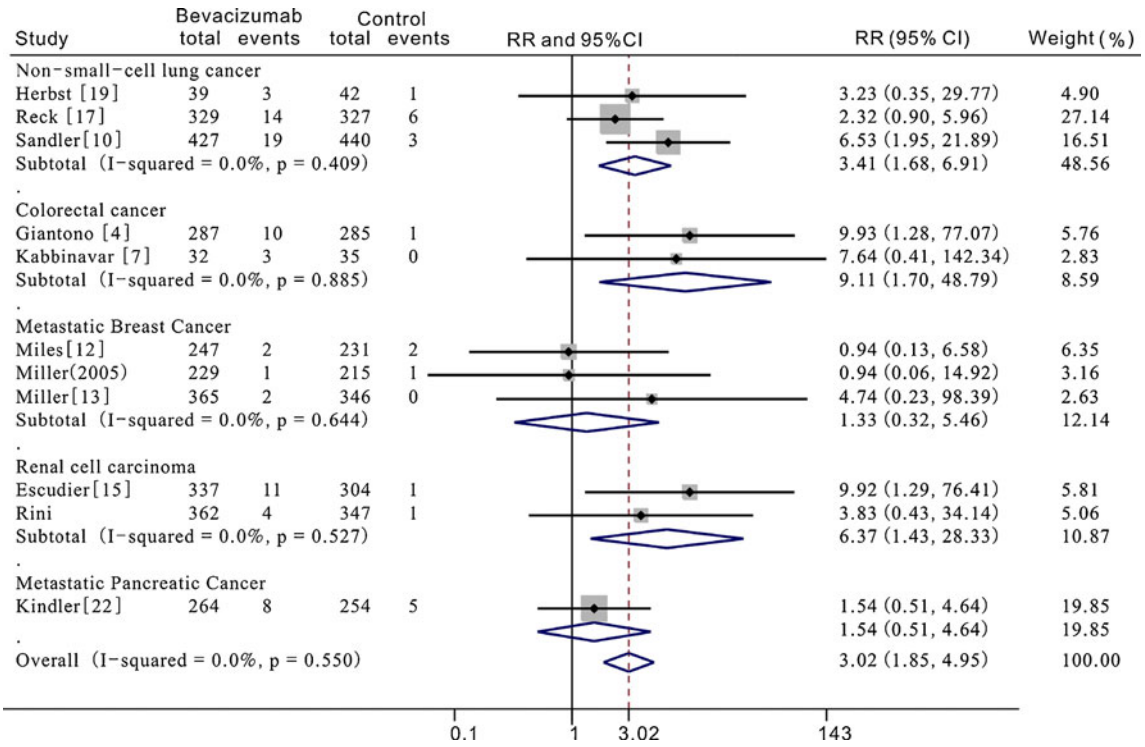

Fig. 5 Meta-analysis of RR of high-grade bleeding based on a comparison of patients receiving high-dose bevacizumab (5 mg/kg per week) and those receiving a non-bevacizumab treatment for cancer

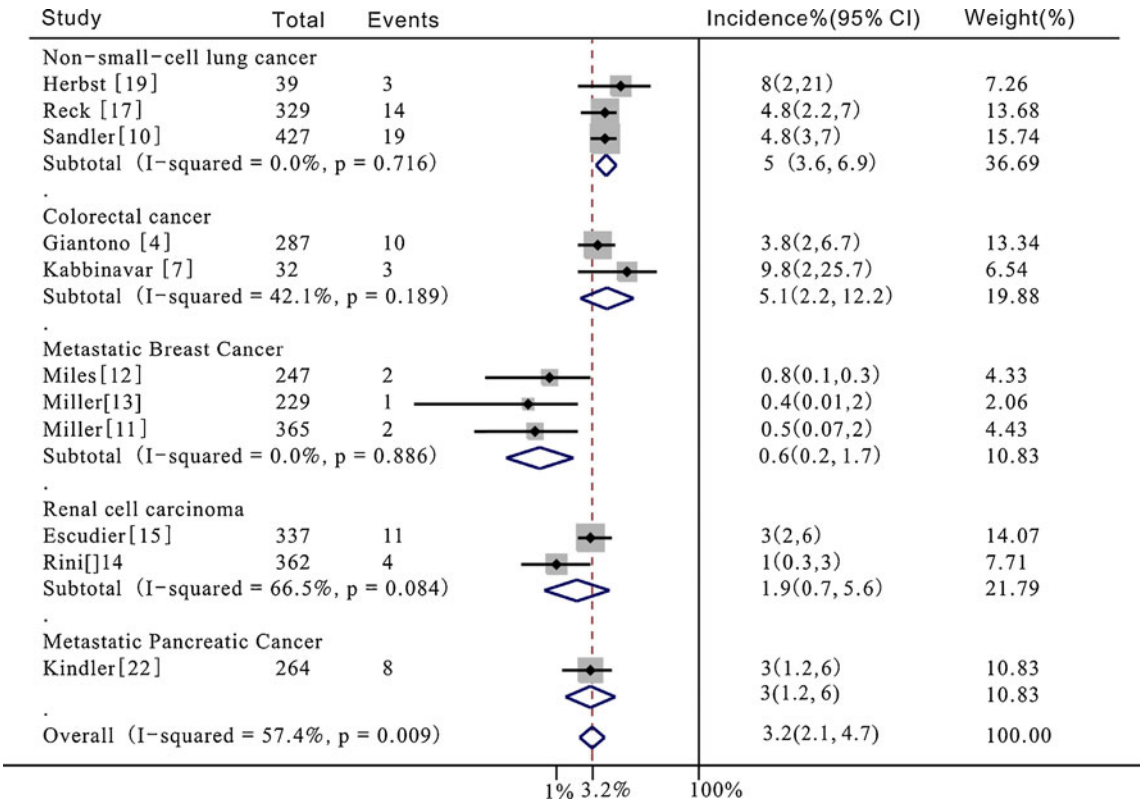

Fig. 6 Meta-analysis of incidence of high-grade bleeding in cancer patients receiving high doses of bevacizumab (5 mg/kg per week)

the dose of bevacizumab was related to the risk of high-grade bleeding. We were unable to identify an association between a dose–response for bevacizumab and high-grade bleeding in any one trial included in the meta-analysis. For example, Miller et al. [13] reported the lowest rate of high-grade bleeding (0.4%) with bevacizumab 5 mg/kg per week, while Cutsem et al. [21] reported the highest rate of high-grade bleeding (7%) with bevacizumab 2.5 mg/kg per week. The findings of our meta-analysis suggest that the increased risk of high-grade bleeding is dose dependent, as the overall RR of high-grade bleeding was found to be greater in patients receiving a dose of 5 mg/kg per week than in those receiving a dose of 2.5 mg/kg per week (Figs. 4, 5). The addition of bevacizumab 5 mg/kg per week to the cancer chemotherapy regimen significantly increased the risk of high-grade bleeding, while the addition of bevacizumab 2.5 mg/kg per week did not.

Our study also showed that the risk of high-grade bleeding with bevacizumab was relatively higher in patients with certain type of tumors who had received bevacizumab (Figs. 5, 6), suggesting that the risk may vary with tumor type. For the dose of 5 mg/kg per week, the overall RR and incidence were relatively higher in patients with non-small-cell lung cancer, renal cell carcinoma, and colorectal cancer (Fig. 5). The potentially higher RR of bevacizumab-related high-grade bleeding in patients with non-small-cell lung cancer is associated with squamous histology, tumor location close to major blood vessels, and tumor necrosis or cavitation [35]. Sandler et al. suggested that baseline cavitation was the main risk factor of high-grade bleeding for patients with non-small-cell lung cancer [36]. Bevacizumab is believed to cause central necrosis and to enlarge the tumor cavity in these patients. This, in combination with the immature blood vessels within the cavity, increases the risk of bleeding. The potentially higher RR of bevacizumab-related high-grade bleeding in patients with renal cell cancer may be due to the unique biology of renal cell cancer itself. Renal cell cancer patients usually have an inactivation of the von-Hippel Lindau (VHL) gene, which could upregulate VEGF [37]. Therefore, blockade of the VEGF pathway in patients with renal cell tumors who have pre-existing upregulated VEGF in the endothelial cell microenvironment may substantially impair endothelial function, thereby increasing the risk of bleeding. In addition, many patients with renal cell cancer have renal insufficiency, resulting in a decreased clearance of bevacizumab. Patients with colorectal cancer also have a higher risk of high-grade bleeding. Flynn et al. reported that the most common site of bevacizumab-related high-grade bleeding in patients with colorectal cancer is the gastrointestinal/rectal tract [38]. These investigators found that patients with primary tumor of the rectum had a higher rate of high-

grade bleeding than did those with primary tumor of the colon, suggesting that the location of the primary cancer may be associated with the risk of high-grade bleeding. However, as yet there is a lack of data on the possible mechanism. Studies focusing on this issue are required.

Although the study recently published by Hapani et al. comprised a meta-analysis of the overall risk of bevacizumab-associated bleeding, the risk factors of bleeding were not clearly elucidated [39]. We obtained similar results in terms of the overall incidence of bevacizumab-associated bleeding as Hapani et al. In contrast to this earlier meta-analysis, we examined 22 RCTs with more patients and paid more attention to the risk factors for the development of bevacizumab-associated high-grade bleeding, an important issue in reducing the risk of occurrence. However, any meta-analysis is not without limitations. First, our findings were affected by the limitations of the individual clinical trials included in the analysis. We attempted to analyze the effect of treatment duration on the incidence of bleeding events, but data on the occurrence of the bleeding event during the course of the respective trial were frequently not reported. Furthermore, the risk of bleeding can be increased by the concurrent use of anti-coagulants (e.g., warfarin), antiplatelet treatment (e.g., aspirin, clopidogrel, ticlopidine), or both. However, such patients are sometimes excluded from clinical trials, even though the use of these drugs is very common in clinical practice, specifically in individuals with malignant disease. Second, heterogeneity is associated with some relevant aspects (such as patient clinical profiles, concurrent chemotherapy, and lengths of follow-up). However, differences among trials are inevitable since each individual trial looks at a different population(s) with different treatment protocols, and there is always some heterogeneity, even within individual trials. But heterogeneity does not preclude pooling of their results because individual patient is directly compared only with other patients within the same trial, and not across the trials [40, 41]. Given this uncertainty resulting from clinical heterogeneity, we performed subgroup analysis in our meta-analysis. Third, although our findings showed that the patients with non-small-cell lung cancer, renal cell carcinoma, and colorectal cancer have a higher risk of high-grade bleeding, this finding might be limited by the small sample size of patients with each of the tumor type. Finally, except for tumor type and bevacizumab dose, other potential risk factors, such as age, race, sex, and history of hematologic diseases, could not be evaluated in our meta-analysis.

In conclusion, despite the limitations of our meta-analysis, we conclude that the addition of bevacizumab to a cancer chemotherapy regimen is associated with a significantly increased risk of developing high-grade bleeding. The risk may be dose-dependent, and it may vary with tumor type. Clinicians should be aware of the possibility that any patient treated with bevacizumab may develop high-grade bleeding, especially in patients at high risk. Future studies are recommended to investigate risk reduction and the possible use of bevacizumab in selected patients.

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Conflict of interest The authors state that they have no conflict of interest.

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