

Does nab-paclitaxel have a higher incidence of peripheral neuropathy than solvent-based paclitaxel? Evidence from a systematic review and meta-analysis



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ABSTRACT

Paclitaxel-induced peripheral neuropathy is a common reason for dose reduction or early cessation of therapy. Nab-paclitaxel was developed to provide additional clinical benefits and overcome the safety drawbacks of solvent-based paclitaxel. However, the incidence of peripheral neuropathy induced by nab-paclitaxel was reported higher than solvent-based paclitaxel but evidence remains inconsistent. Therefore, we conducted a meta-analysis to compare the incidence and severity of peripheral neuropathy between nab-paclitaxel and solvent-based paclitaxel mono-chemotherapy. In total, 24 articles were included in this meta-analysis. Results revealed the incidence of peripheral neuropathy induced by nab-paclitaxel was higher than solvent-based paclitaxel. The dosage and assessment method could influence the comparison of the incidence and severity of peripheral neuropathy between nab-paclitaxel and solvent-based paclitaxel. Current evidence suggests the incidence of peripheral neuropathy induced by nab-paclitaxel was higher than solvent-based paclitaxel among cancer patients received mono-chemotherapy. When received nab-paclitaxel, more attention should be paid to peripheral neuropathy.

1. Introduction

Chemotherapy-induced peripheral neuropathy is a severe adverse effect observed in up to 80% of patients during treatment with anti-neoplastic drugs and leading to dose modification and can lead to discontinuation of chemotherapy (Sisignano et al., 2014). As a member of chemotherapy agents, paclitaxel is classified as a microtubule-stabilising agent and is effective in treating the various types of solid tumors such as breast, ovarian and lung cancer (Tolaney et al., 2015; Armstrong et al., 2006; Kellokumpu-Lehtinen et al., 2013; Camidge et al., 2014; Kampan et al., 2015). However, peripheral neuropathy is the main non-haematological toxicity of paclitaxel and affecting the therapeutic efficacy and clinical benefits (Mielke et al., 2006). A lot of studies have reported the incidence of peripheral neuropathy in patients received paclitaxel, however, with a large range in various studies (van Herpen et al., 2010; Kosmidis et al., 2007).

The underlying mechanism of peripheral neuropathy induced by paclitaxel is not entirely understood and was reported to be associated with oxidative stress and abnormalities of sphingolipids (Kramer et al., 2015; Kiya et al., 2011; Duggett et al., 2016; Cavaletti et al., 2000; Argyriou et al., 2008). Several studies reported that the side effect of peripheral neuropathy was associated with both the solvent (Cremophor EL) and paclitaxel itself (Campos et al., 2014). To provide additional clinical benefits and overcome the safety drawbacks of solvent-based paclitaxel, nab-paclitaxel (an albumin-bound formulation of paclitaxel) was developed (Cecco et al., 2014). Nab-paclitaxel is a water-soluble and Cremophor EL-free formulation of paclitaxel which has no toxicity induced by Cremophor EL. However, studies found the incidence of peripheral neuropathy induced by nab-paclitaxel seemed higher than solvent-based paclitaxel among cancer patients, although the results were still inconsistent (Untch et al., 2016; Guo et al., 2015; Seidman et al., 2013).

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A previous meta-analysis had investigated the incidence and relative risk (RR) of peripheral neuropathy among cancer patients received nab-paclitaxel (Peng et al., 2015). The results indicated that the overall incidence of all-grade and high-grade peripheral neuropathy were 51.0% (95% CI: 45.1–57.6%) and 12.4% (9.8–15.7%), respectively. In addition, their results showed that the RRs of peripheral neuropathy of nab-paclitaxel compared to taxanes (paclitaxel and docetaxel) were not increased. However, the studies they included in their meta-analysis contained patients administered with other chemotherapy simultaneously. This could influence the authentic incidence of peripheral neuropathy as other chemotherapy agents such as vincristine could also cause side effect of peripheral neuropathy. In addition, other concomitant diseases such as diabetes could also induced peripheral neuropathy while the study didn't take these factors into account.

To our knowledge, the studies reported the incidence and severity of peripheral neuropathy among cancer patients received nab-paclitaxel or solvent-based paclitaxel mono-chemotherapy has not been performed a statistical pooling. Therefore, we conducted a meta-analysis to validate the incidence of peripheral neuropathy induced by nab-paclitaxel or solvent-based paclitaxel and to compare the incidence and severity of peripheral neuropathy between nab-paclitaxel and solvent-based paclitaxel among cancer patients.

2. Methods

2.1. Data sources and search strategy

We searched PubMed, Ovid EMBASE databases, Web of Science and Cochrane Library databases for articles published before June 20th, 2017. Combining the keywords and free words, the searches terms used for the search were “Paclitaxel OR taxol OR PTX OR Taxane OR solvent-based paclitaxel OR Nab-paclitaxel OR nanoparticle albumin-bound paclitaxel OR albumin-bound paclitaxel OR nab-P OR Abraxane OR ABI-007 OR chemotherapy” and “cancer OR carcinoma OR neoplasm” and “Incidence OR Risk OR RR OR relative risk” and “Peripheral neuropathy OR PIPN OR neurotoxicity OR nerve toxicity OR peripheral nerve toxicity OR CIPN OR adverse reaction OR side effect OR adverse effect OR ADR”. The detailed search terms and strategies were shown in Supplementary Table 1. The published articles were limited to English-language and human study. Additionally, two authors manually screened the citation lists of retrieved articles independently. All eligible articles were checked according to a Newcastle-Ottawa Quality assessment Scale developed previously (Stang, 2010).

2.2. Inclusion and exclusion criteria

Inclusion criteria of this meta-analysis were as follows: (1) independently published study investigating the incidence of peripheral neuropathy among cancer patients received nab-paclitaxel or solvent-based paclitaxel mono-chemotherapy; (2) the literature should be published with enough information. Exclusion criteria included: (1) case report or case series; (2) reviews; (3) the cases of the articles were fewer than 20 patients; (4) studies with patients received other chemotherapy drugs simultaneously; (5) studies included patients with other concomitant diseases such as diabetes which could also induce peripheral neuropathy; (6) studies without enough information; (7) repeated or overlapping publications.

2.3. Data extraction and quality assessment

Data extraction from the eligible studies was independently performed by two evaluators. Two other evaluators resolved any disagreements regarding the data extraction. We extracted the incidence and severity of peripheral neuropathy from the safety profile in each study. The majority of the eligible studies used the NCI-CTC assessment

method on peripheral neuropathy. Although the versions of NCI-CTC used in these included studies were various, the assessment on peripheral neuropathy was generally consistent (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). The grading of peripheral neuropathy was as follows: grade I, asymptomatic, loss of deep tendon reflexes or paraesthesia; grade II, moderate symptoms, limiting instrumental activities of daily living (ADL); grade III, severe symptoms, limiting self care ADL; and grade IV, life-threatening consequences, urgent intervention indicated. Grade I–IV and III–IV of peripheral neuropathy were defined as all-grade and high-grade peripheral neuropathy, respectively. The incidence and 95% confidence interval (CI) of patients with adverse outcomes were retrieved in each study.

The collected detailed information of each articles mainly included the name of first author, publication year, ethnicity, country, cancer types of the patients, dose and schedule of nab-paclitaxel or solvent-based paclitaxel, method of assessment on peripheral neuropathy. If several publications were overlapped, the most recent publication was selected to be further analyzed. Items were treated as ‘NA (not available)’, if data from the above categories were not reported in the study.

The nine-star Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of each eligible study. A study with an NOS score ≥ 7 would be considered as a high quality. Additionally, the information would be examined and adjudicated independently by an investigator after data extraction and assessment.

2.4. Statistical analysis

From the eligible studies, the overall incidence of peripheral neuropathy among cancer patients received nab-paclitaxel or solvent-based paclitaxel mono-chemotherapy was carried out by the R software (version 3.4.1) and estimated basing on a fixed-effects model or random-effects model based on the study heterogeneity. The statistical heterogeneity among studies included in our meta-analysis was assessed with the Q statistic and inconsistency was quantified with the I^2 statistic. The heterogeneity was judged as statistically significant when P less than 0.10. The fixed-effects model was used when the P value of heterogeneity was greater than 0.10, otherwise, the random-effects model was used. An inverse variance statistical method was used to calculate the pooled incidence. The results of the overall incidence of peripheral neuropathy were presented using forest plots with exact binomial 95% confidence intervals (CIs). A P value less than 0.05 was considered statistically different.

The consistency and quality of the results were assessed by sensitivity analysis. The potential publication bias was evaluated by the funnel plot and Egger's test.

2.5. Results

A total of 12,073 publications were initially retrieved in this study (Fig. 1). According to the inclusion and exclusion criteria of this meta-analysis, 28 potential studies were included for full-text view. With further screening, 24 studies reported the incidence of peripheral neuropathy among cancer patients received nab-paclitaxel or solvent-based paclitaxel mono-chemotherapy were identified (Akerley et al., 2003; Alberts et al., 2012; Damascelli et al., 2007; duBois et al., 1999; Ducreux et al., 2017; Dunder et al., 2005; Eisenhauer et al., 1994; Forastiere et al., 1998; Horton et al., 2008; Juan et al., 2007; Koizumi et al., 2009; Kraff et al., 2015; Mielke et al., 2005; Noda et al., 1996; Omura et al., 2003; Paik et al., 2011; Prados et al., 1996; Rizvi et al., 2008; Tamura et al., 1995; Tay and Thilagam, 1998; Tsimberidou et al., 2011; Tsuyuki et al., 2017; Vecchio et al., 2013; Winer et al., 2004).

The main characteristics included the name of first author, publication year, ethnicity, country, cancer types of the patients, dose and schedule of nab-paclitaxel or solvent-based paclitaxel and assessment method of peripheral neuropathy (summarized in Table 1). Among the eligible 24 articles, there were 7 articles investigated on the incidence

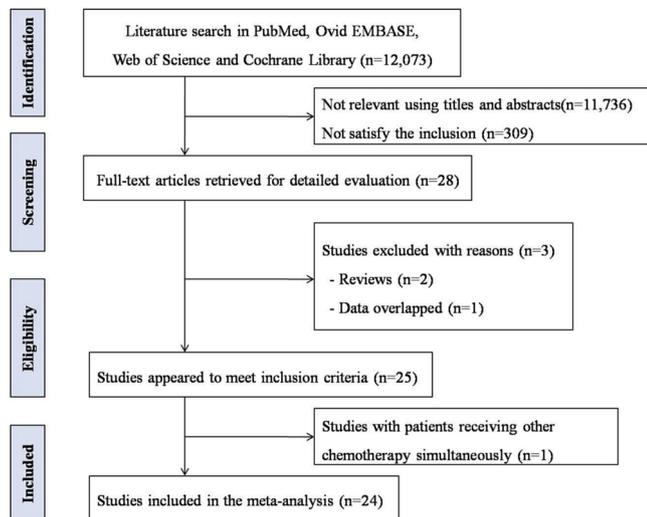


Fig. 1. Flow diagram of search and selection process.

of peripheral neuropathy induced by nab-paclitaxel, while 17 articles on paclitaxel. Among the 7 articles about nab-paclitaxel, 6 and 7 articles reported the incidence of all-grade and high-grade peripheral neuropathy, respectively. Meanwhile, among the 17 articles reported solvent-based paclitaxel, both 15 articles reported the incidence of all-grade and high-grade peripheral neuropathy, respectively.

2.6. Incidence of peripheral neuropathy induced by nab-paclitaxel/ solvent-based paclitaxel

The overall incidence of all-grade and high-grade peripheral neuropathy among cancer patients received nab-paclitaxel/ solvent-based paclitaxel were shown in Fig. 2a and b, respectively. The results of

statistic analysis showed that the incidence of all-grade peripheral neuropathy in cancer patients received nab-paclitaxel and solvent-based paclitaxel were 65% (95%CI: 47%–80%) and 54% (95%CI: 44%–63%), respectively. Additionally, the incidence of high-grade peripheral neuropathy between nab-paclitaxel and solvent-based paclitaxel were 16% (95%CI: 11%–23%) and 5% (95%CI: 3%–8%), respectively, with a statistical difference (P < 0.001).

2.7. Subgroup analysis by the administration dosage

To explore the relationship between peripheral neuropathy and different doses of nab-paclitaxel/ solvent-based paclitaxel, subgroup analysis was performed by administration dosage. We defined the dose less than 150 mg/m² was low-dose while equal or greater than 150 mg/m² was high-dose. The results of subgroup analysis were showed in Fig. 3.

In the low-dose arm, we compared the incidence of peripheral neuropathy between nab-paclitaxel and solvent-based paclitaxel. Results showed that in the low-dose arm, the incidence of peripheral neuropathy induced by nab-paclitaxel was significant greater than solvent-based paclitaxel (all-grade: nab-paclitaxel vs. solvent-based paclitaxel: 66% vs. 40%, P = 0.0048; high-grade: nab-paclitaxel vs. solvent-based paclitaxel: 14% vs. 3%, P = 0.0001; Fig. 3a and b). In the high-dose arm, the incidence of peripheral neuropathy induced by nab-paclitaxel was greater than solvent-based paclitaxel in tendency (all-grade: nab-paclitaxel vs. solvent-based paclitaxel: 64% vs. 58%, P > 0.05; high-grade: nab-paclitaxel vs. solvent-based paclitaxel: 18% vs. 10%, P > 0.05; Fig. 3c and d).

2.8. Subgroup analysis by the assessment method of peripheral neuropathy

The different assessment methods of peripheral neuropathy might influence the accuracy of the incidence of peripheral neuropathy induced by nab-paclitaxel and solvent-based paclitaxel. Among the included studies, the majority used National Cancer Institute-Common

Table 1 Main characteristics of the studies included in meta-analysis.

Study	Ethnicity	Country	Cancer Types	Dose and frequency	Median Cycles	Assessment method	Treatment Arm
Akerley et al. (2003)	Caucasian	USA	Lung	150 mg/m ² , 3h, weekly	4	NA	Paclitaxel
Alberts et al. (2012)	Caucasian	USA	Cervix	125 mg/m ² , Q1W × 3	4 (1–15)	NCI-CTCAE v3.0	Nab-paclitaxel
Damascelli et al. (2007)	Caucasian	Italy	Oral, oropharynx	150/180/230mg/m ² , Q3W	2-4	WHO criteria	Nab-paclitaxel
du Bois et al. (1999)	Caucasian	Germany	Ovarian, Breast	135/175 mg/m ² , 3h/24h	6	Questionnaire	Paclitaxel
Ducieux et al. (2017)	Caucasian	France	mCRC	125 mg/m ² , Q1W × 3	≥ 1dose	NCI-CTCAE v4.0.	Nab-paclitaxel
Dunder et al. (2005)	Caucasian	Turkey	Ovarian	80 mg/m ² , 1h, weekly	3	NA	Paclitaxel
Eisenhauer et al. (1994)	Caucasian	Belgium	Ovarian	135mg/m ² ;175mg/m ² , 3h /24h	6	WHO criteria	Paclitaxel
Forastiere et al. (1998)	Caucasian	USA	Head and neck	250 mg/m ² , 24h, Q3W 250-500 mg/m ² , Q3W;	4 (1-18)	NCI-CTCAE	Paclitaxel
Horton et al. (2008)	Caucasian	USA	Leukemia	105-200mg/m ² , Q1W × 3	≥ 1	NCI-CTCAE v2.0.	Paclitaxel
Juan et al. (2007)	Caucasian	Spain	NSCLC	80 mg/m ² , 1h, weekly	10	NCI-CTCAE	Paclitaxel
Koizumi et al. (2009)	Asian	Japan	Gastric	140 mg/m ² , Q2W × 2	≥ 2	NCI-CTCAE v 3.0.	Paclitaxel
Kraff et al. (2015)	NA	NA	Cervical, etc	50–130 mg/m ² , 1-3h, weekly	NA	NCI-CTCAE v4.0.	Paclitaxel
Mielke et al. (2005)	Caucasian	Germany	Breast, lung, etc.	100 mg/m ² , 1 or 3h	1-2	NCI-CTCAE	Paclitaxel
Noda et al. (1996)	Asian	Japan	Ovarian	3h	NA	NA	Paclitaxel
Omura et al. (2003)	Caucasian	USA	Ovarian	175 or 250 mg/m ² , 24h, Q3W	6	GOG-CTC	Paclitaxel
Paik et al. (2011)	Caucasian	USA	NSCLC	125 mg/m ² , 2h, Q1W × 3	4	NIH-CTCAE v3.0	Nab-paclitaxel
Prados et al. (1996)	Caucasian	USA	Glioma	210-240mg/m ² , 3h, Q3W	1-12	NCI-CTCAE	Paclitaxel
Rizvi et al. (2008)	Caucasian	USA	NSCLC	125 mg/m ² , 30min, Q1W × 3	4	NCI-CTCAE v3.0	Nab-paclitaxel
Tamura et al. (1995)	Asian	Japan	Lung, breast, etc	105-270mg/m ² 3h, Q3W	NA	ECOG CTC	Paclitaxel
Tay and Thilagam (1998)	Asian	Singapore	Ovarian	200 mg/m ² , 3 h, Q4W	4	NA	Paclitaxel
Tsimberidou et al. (2011)	Caucasian	USA	Gastric, prostate	150-275 mg/m ² , 24 h, Q4W	1	NCI-CTCAE v3.0	Paclitaxel
Tsuyuki et al. (2017)	Asian	Japan	Breast	260 mg/m ²	NA	NCI-CTCAE v4.0	Nab-paclitaxel
Vecchio et al. (2013)	Mixed	Multinational	Melanoma	150 mg/m ² , Q1W × 3	NA	Standardized MedDRA Query	Nab-paclitaxel
Winer et al. (2004)	Caucasian	USA	Breast	175/210/250mg/m ² ; 3h, Q3W	3	NCI-CTCAE	Paclitaxel

Q1W × 3: days 1, 8, and 15 of a 28-day cycle; Q2W × 2: days 1, 15 of a 28-day cycle; Q3W: every 3weeks; Q4W: every 4weeks; 30 min, 1 h, 3 h, 24 h infusion; NCI-CTC: National Cancer Institute—Common Terminology Criteria; CTCAE: Common Terminology Criteria for Adverse Events; GOG CTC: Gynecologic Oncology Group common toxicity criteria; QST: Quantitative Sensory Testing; PNQ: Patient Neurotoxicity Questionnaire; WHO criteria: World Health Organization criteria; ECOG CTC: Eastern Cooperative Oncology Group Common Toxicity Criteria; NSCLC: non-small-cell lung cancer; mCRC: metastatic colorectal cancer; NA: not available.

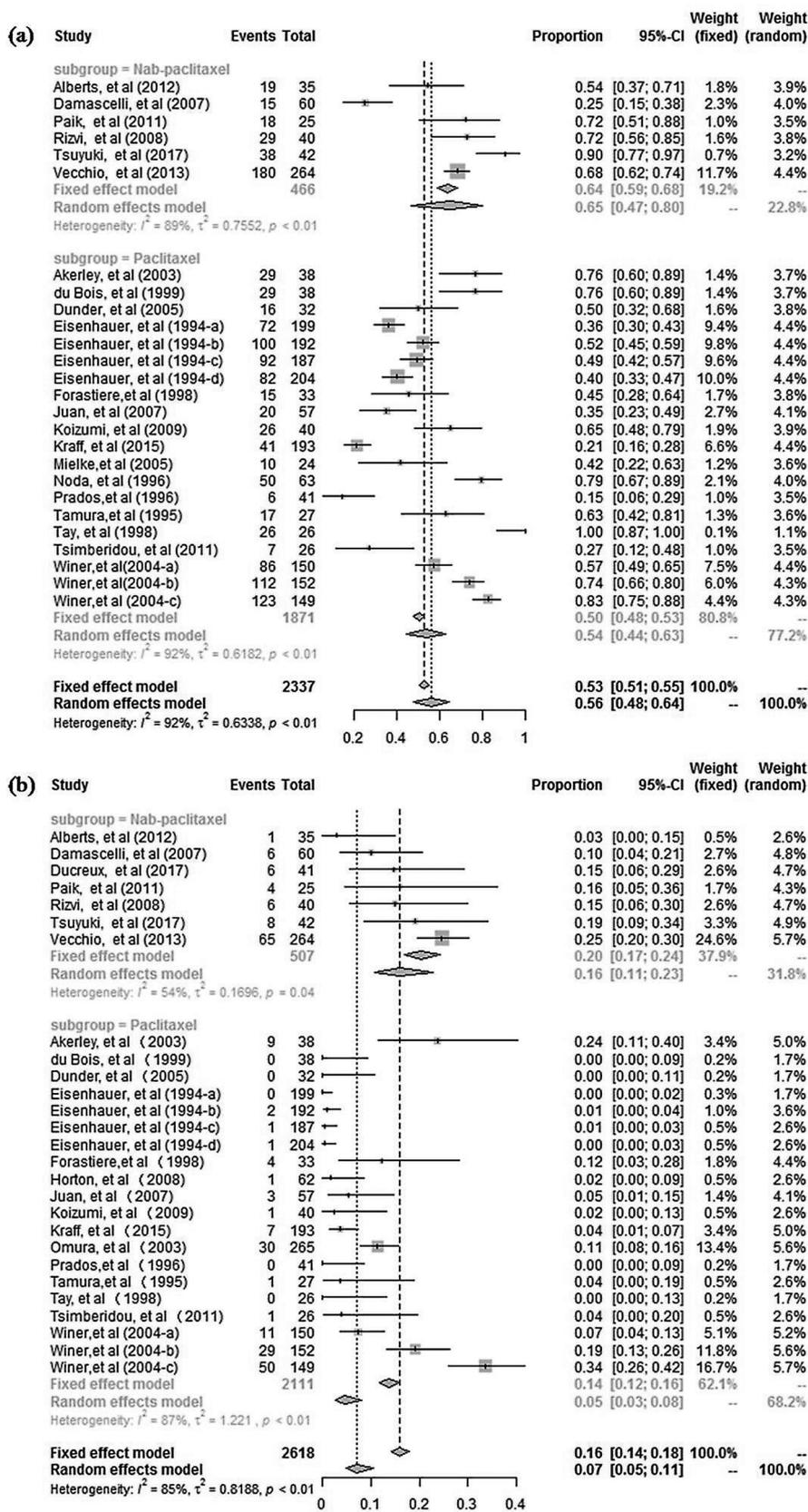


Fig. 2. Forest plot of the comparison on the incidence of peripheral neuropathy between nab-paclitaxel and solvent-based paclitaxel among cancer patients. (a) All-grade peripheral neuropathy; (b) High-grade peripheral neuropathy

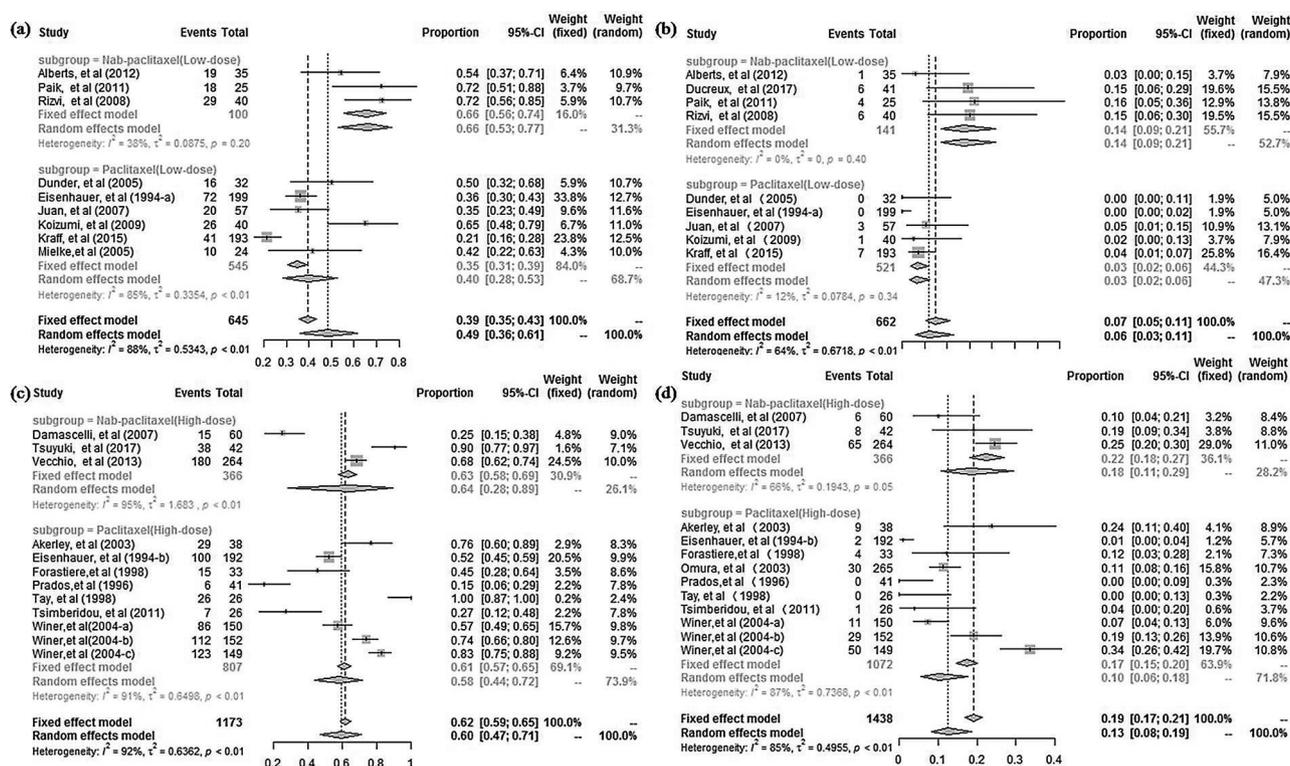


Fig. 3. Forest plot of the subgroup analysis by the administration dosage of nab-paclitaxel/ solvent-based paclitaxel. (a) Incidence of all-grade peripheral neuropathy in low-dose arm: nab-paclitaxel vs. solvent based-paclitaxel; (b) Incidence of high-grade peripheral neuropathy in low-dose arm: nab-paclitaxel vs. solvent based-paclitaxel; (c) Incidence of all-grade peripheral neuropathy in high-dose arm: nab-paclitaxel vs. solvent based-paclitaxel; (d) Incidence of high-grade peripheral neuropathy in high-dose arm: nab-paclitaxel vs. solvent based-paclitaxel

Terminology Criteria (NCI-CTC) assessment method. Therefore, we conducted a statistic analysis among studies with NCI-CTC assessment method.

The analysis showed that the incidence of all-grade peripheral neuropathy induced by nab-paclitaxel versus solvent-based paclitaxel were 73% [56%–86%] vs. 46% [30%–63%] ($P = 0.028$; Fig. 4a). The incidence of high-grade peripheral neuropathy induced by nab-paclitaxel versus solvent-based paclitaxel were 15% [10%–21%] vs. 7% [3%–15%] ($P = 0.068$; Fig. 4b).

2.9. Qualitative assessment

Quality assessment of the 24 eligible studies was performed using the nine-star Newcastle–Ottawa Scale (NOS) (Supplementary Table 2). The average NOS score of the 24 eligible studies was 7.13 (ranged from 6 to 8) indicating that the majority of the eligible studies were with high quality.

2.10. Sensitivity analysis

The sensitivity analysis was performed to evaluate the results of the incidence of peripheral neuropathy among cancer patients received nab-paclitaxel/ solvent-based paclitaxel. The sensitivity analysis showed that no significant alterations of the overall incidence were existed indicating that the results of the incidence of peripheral neuropathy in cancer patients received nab-paclitaxel/ solvent-based paclitaxel were relative stable and reliable (Supplementary Table 3).

2.11. Publication bias

The publication bias of the eligible studies was assessed by the funnel plot (shown in Fig. 5) and Egger’s test. The shape of the funnel plot of the incidence of high-grade peripheral neuropathy induced by

solvent-based paclitaxel was approximately asymmetrical. Additionally, the Egger’s test suggested that publication bias was existed ($P = 0.01$). The other three funnel plots were symmetrical and no publication bias was existed (Egger’s test, $P > 0.05$).

3. Discussion

Peripheral neuropathy has emerged as a dose-limiting toxicity that is encountered with all taxanes and is a feature of mitotic inhibitors in general (Mielke et al., 2006). The mechanisms of peripheral neuropathy induced by taxanes are not entirely clear. Recently, several studies indicated that two factors, the solvents which are Cremophor EL for paclitaxel and polysorbate 80 for docetaxel, and the taxanes itself could induce the side effect of peripheral neuropathy (Campos et al., 2014).

Nab-paclitaxel is a Cremophor EL-free formulation of paclitaxel and was first approved by the FDA in 2005 for the treatment of metastatic breast cancer (Kundranda and Niu, 2015). Nab-paclitaxel was demonstrated at a higher maximum tolerated dose of 260 mg/m² compared with solvent-based paclitaxel at 175 mg/m² in a 3-weekly schedule by a randomised phase III trial (Gradishar et al., 2005). With avoiding use of Cremophor EL and being more tumor-targeted, the incidence of peripheral neuropathy induced by nab-paclitaxel was generally lower than solvent-based paclitaxel theoretically. However, the results are still conflicting. Several studies reported that nab-paclitaxel could induce a less severe course of peripheral neuropathy, while some studies indicated that the incidence and severity of peripheral neuropathy induced by nab-paclitaxel was higher than that induced by solvent-based paclitaxel. Additionally, the incidence and severity of peripheral neuropathy induced by nab-paclitaxel and solvent-based paclitaxel had no differences reported in some studies. Although a previous meta-analysis was conducted to explore the incidence and severity of peripheral neuropathy induced by nab-paclitaxel, the study didn’t take the influence of other chemotherapy agents and some comorbidities such as

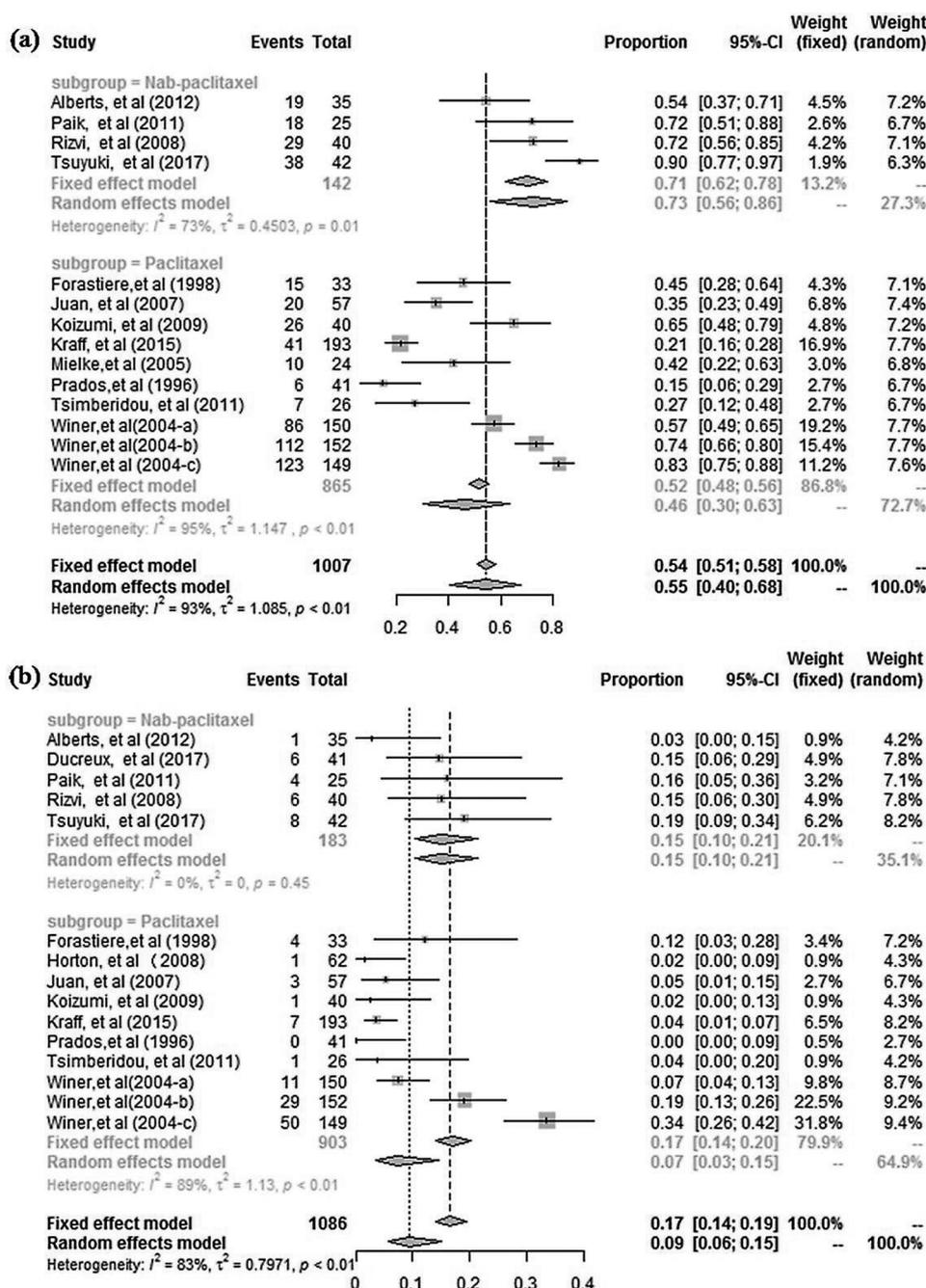


Fig. 4. Forest plot of the comparison on the incidence of peripheral neuropathy between nab-paclitaxel and solvent-based paclitaxel among studies with the same method of assessment on peripheral neuropathy. (a) Incidence of all-grade peripheral neuropathy induced by nab-paclitaxel versus solvent-based paclitaxel; (b) Incidence of high-grade peripheral neuropathy induced by nab-paclitaxel versus solvent-based paclitaxel.

diabetes into account (Peng et al., 2015).

Based on the inconsistent conclusions, we conducted a systemic review and meta-analysis to compare the incidence and severity of peripheral neuropathy induced by nab-paclitaxel and solvent-based paclitaxel among cancer patients who received mono-chemotherapy. We tried to exclude the other factors as much as possible that could cause peripheral neuropathy. After collecting historical cases and comparing the incidence of peripheral neuropathy between nab-paclitaxel and solvent-based paclitaxel, we found evidence that nab-paclitaxel regimen showed higher incidence of peripheral neuropathy, while the incidence of peripheral neuropathy of solvent-based paclitaxel were relatively lower. When conducted a statistic analysis among studies

with the same method of assessment on peripheral neuropathy (NCI-CTC), the difference was more significant (73% vs. 46%, $P < 0.05$). Furthermore, the high-grade peripheral neuropathy induced by nab-paclitaxel was significant higher than that induced by solvent-based paclitaxel (16% vs. 5%, $P < 0.001$).

Subgroup analysis was performed according to the administration dosage. Results of subgroup analysis indicated that the administration dosage has a great impact on the comparison of the incidence and severity of peripheral neuropathy between nab-paclitaxel and solvent-based paclitaxel. The incidence of peripheral neuropathy of nab-paclitaxel was significant greater than solvent-based paclitaxel in the low-dose arm, while the incidence of peripheral neuropathy of the two

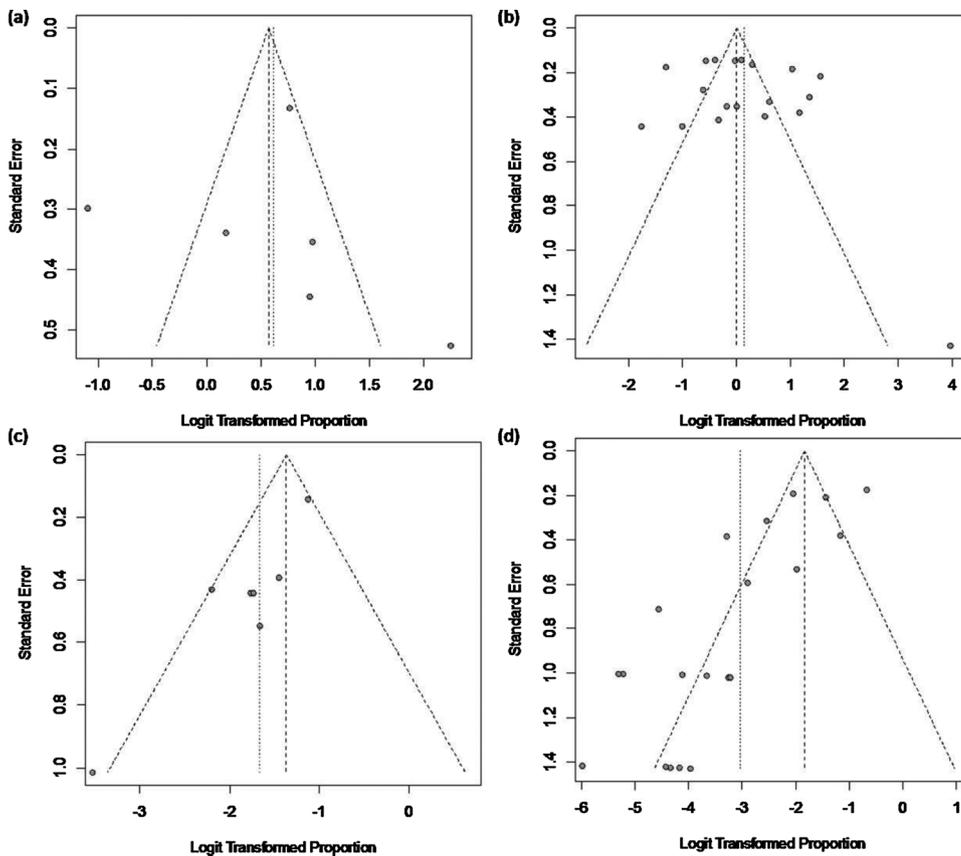


Fig. 5. Funnel plot of incidence and severity of peripheral neuropathy induced by nab-paclitaxel/ solvent-based paclitaxel for publication bias.

- (a) Incidence of all-grade peripheral neuropathy for nab-paclitaxel;
 (b) Incidence of all-grade peripheral neuropathy for solvent-based paclitaxel;
 (c) Incidence of high-grade peripheral neuropathy for nab-paclitaxel;
 (d) Incidence of high-grade peripheral neuropathy for solvent-based paclitaxel.

formulations of paclitaxel was not significantly different in the high-dose arm.

The mechanisms of the higher incidence and severity of peripheral neuropathy induced by nab-paclitaxel compared with solvent-based paclitaxel were still unclear. We speculate that this phenomenon could be explained by some reasons. On the one hand, the doses, schedule and cycles are different in these studies which are obvious confounders. The ethnicity and cancer types of patients as well as the number of patients are also variable. On the other hand, the different drug transport mechanisms of nab-paclitaxel and solvent-based paclitaxel might cause the different incidence and severity of peripheral neuropathy. Since nab-paclitaxel is the nanoparticle albumin-bound paclitaxel, albumin could serve as a carrier for drug internalization in cells. It has been confirmed that the uptake of nab-paclitaxel can be facilitated by the interaction of albumin with the cell surface receptor gp60 which is expressed on endothelial cells (Tiruppathi et al., 1997). This could promote the internalization of the drug-albumin complex into caveolae in tumor interstitium and the succedent bind with secreted protein acidic and rich in cysteine (SPARC) leading to a higher accumulation of paclitaxel. As the SPARC is also expressed in neuronal and neuroglial cells, we speculate that the paclitaxel accumulation of nab-paclitaxel might be higher than that of solvent-based paclitaxel in these cells. In our *in vitro* study, we have demonstrated this speculation which might be reported in a subsequent article. Why the incidence of peripheral neuropathy of the two formulations of paclitaxel in low-dose arm was more significantly different than that in high-dose arm? We speculate that the paclitaxel uptake rate and accumulation of nab-paclitaxel in cells are faster and greater than that of solvent-based paclitaxel in low doses. As the dosage increases, the cell surface receptor gp60 and SPARC would be gradually reached saturation. Therefore, the paclitaxel accumulation of nab-paclitaxel in neural cells would no longer increase after the saturation of the receptor gp60 and SPARC have been reached. We will verify this speculation in the subsequent experiment.

There are some limitations existed in this meta-analysis. Firstly, some relevant studies were excluded in the meta-analysis because of the incomplete raw data or publication limitations. Secondly, although we tried our best to exclude the other factors that could cause peripheral neuropathy, the heterogeneity among the included studies, resulting from different clinical characteristics, such as ethnicity, cancer types, dosage, schedule or cycles of nab-paclitaxel or solvent-based paclitaxel, might affect the analysis results. We found that heterogeneity among studies existed in overall comparisons. After subgroup analysis was performed by administration dosage of nab-paclitaxel/ solvent-based paclitaxel, the heterogeneity was effectively decreased or removed in some arms. Thirdly, publication bias is a major concern in all forms of meta-analysis and is existed in our meta-analysis which might cause the imprecise results. Furthermore, we could not analyze the impact of the ethnicity, cancer types, treatment cycles or other potential confounders on the incidence and severity of peripheral neuropathy induced by nab-paclitaxel or solvent-based paclitaxel because of the limited articles.

In conclusion, our meta-analysis indicates that the incidence and severity of peripheral neuropathy induced by nab-paclitaxel are higher than solvent-based paclitaxel. We recommend that more attention should be paid to the peripheral neuropathy when patients received nab-paclitaxel. Further large prospective studies with clear adjustment for confounders are warranted.

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Conflicts of interest

None of the authors has any conflict of interest to disclose.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.critrevonc.2019.04.021>.

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