Systematic Review and Meta-Analysis

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The efficacy of gefitinib supplementation for breast cancer

A meta-analysis of randomized controlled studies

Jing Ye, BA[a], Tian Tian, MD[b,*], Xiaopin Chen, MD[b]

Abstract

Introduction: The efficacy of gefitinib supplementation for breast cancer remains controversial. We conduct a systematic review and meta-analysis to explore the influence of gefitinib supplementation vs placebo on the efficacy of breast cancer.

Methods: We have searched PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases through February 2019 and included randomized controlled trials assessing the effect of gefitinib supplementation vs placebo on overall response for breast cancer patients. This meta-analysis was performed using the random-effect model.

Results: Seven randomized controlled trials involving 927 patients were included in the meta-analysis. Overall, compared with control group for breast cancer, gefitinib supplementation revealed no obvious impact on complete response (risk ration [RR] = 1.19; 95% confidence interval [CI] = 0.58 to 2.44; $P = .63$), progressive disease (RR = 0.81; 95% CI = 0.59–1.11; $P = .18$), partial response (RR = 0.67; 95% CI = 0.36–1.25; $P = .21$), stable disease (RR = 1.02; 95% CI = 0.65–1.60; $P = .92$), nausea or vomiting (RR = 0.99; 95% CI = 0.73–1.33; $P = .93$), but was associated with increased incidence of diarrhea (RR = 2.80; 95% CI = 2.23–3.52; $P < .00001$), decreased incidence of hot flash (RR = 0.53; 95% CI = 0.37–0.78; $P = .001$), and improved incidence of adverse events (RR = 1.12; 95% CI = 1.05–1.19; $P = .0006$).

Conclusions: Gefitinib supplementation may provide no positive effect on complete response, progressive disease, partial response or stable disease for breast cancer patients, but with the increase in adverse events.

Abbreviations: EGFR = epidermal growth factor receptor, CI = confidence interval, RCTs = randomized controlled trials, RR = risk ratio.

Keywords: breast cancer, gefitinib supplementation, overall response, randomized controlled trials

1. Introduction

Many patients with breast cancer have the positive expression of estrogen (ER) receptor,[1–3] but endocrine therapy is effective in only half of primary breast cancer.[4,5] Several mechanisms may account for the reduced effectiveness of endocrine therapy. Epidermal growth factor receptor (EGFR) is commonly expressed in breast cancer, indicating a poor prognosis and failure of responding to endocrine therapy.[6,7] Immunohistochemical analyses reveal that 30% of ER-positive tumors are positive for EGFR, and this proportion is up to 51% to 77% in some cases.[8–10]

Gefitinib, a 4-anilinoquinazolone, is known as a well-tolerated inhibitor of EGFR, and produces objective responses in lung cancer.[11] In patients with metastatic colorectal cancer, EGFR has strong correlation with response to anti-EGFR treatment.[12] The presence of specific mutations in colorectal cancer and breast cancer were rarely found.[9] Gefitinib was reported to induce the growth inhibition of endocrine-resistant MCF-7 breast cancer cells via reducing AKT and MAPK phosphorylation, and produced a synergistic effect with tamoxifen administration.[13,14]

However, current evidence is insufficient for routine clinical use of gefitinib supplementation for breast cancer, although several studies have reported the efficacy of gefitinib in these patients.[15–18] To our knowledge, this study is the first meta-analysis of randomized controlled trials (RCTs) to assess the impact of gefitinib supplementation on overall response in patients with breast cancer.

2. Materials and methods

This systematic review and meta-analysis were performed based on the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement and Cochrane Handbook for Systematic Reviews of Interventions.[19,20] No ethical approval and patient consent were required because all analyses were based on previous published studies.

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The authors have no conflicts of interests to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

[a] Department of Surgery, Chongqing Yongchuan Health Center for Women and Children, [b] Department of General Surgery, Yongchuan Hospital of Chongqing Medical University, Chongqing, China.

[*] Correspondence: Tian Tian, No. 439 Xuanhua Road, Yongchuan district, Chongqing 402160, China (e-mail: tiantianis@163.com).

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2.1. Literature search and selection criteria

We systematically searched several databases including PubMed, EMbase, Web of science, EBSCO, and the Cochrane library from inception to February 2019 with the following keywords: "gefitinib," and "breast cancer." The reference lists of retrieved studies and relevant reviews were also hand-searched and the process above was performed repeatedly in order to include additional eligible studies.

The inclusion criteria were presented as follows:

(1) study design was RCT,
(2) patients were diagnosed with breast cancer, and
(3) intervention treatments were gefitinib supplementation vs placebo.

Patients with unstable or uncompensated respiratory, cardiac, hepatic, or renal disease were excluded.

2.2. Data extraction and outcome measures

Some baseline information was extracted from the original studies, and they included first author, number of patients, age, the number of positive estrogen receptor, progesterone receptor and human EGFR 2, detail methods in 2 groups. Data were extracted independently by 2 investigators, and discrepancies were resolved by consensus. We contacted the corresponding author to obtain the data when necessary.

The primary outcomes were complete response and progressive disease. Secondary outcomes included partial response, stable disease, nausea and vomiting, diarrhea, hot flash, and adverse events.

2.3. Quality assessment in individual studies

The methodological quality of each RCT was assessed by the Jadad Scale which consisted of 3 evaluation elements: randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points).[21] One point was allocated to each element if they were conducted and mentioned appropriately in the original article. The score of Jadad Scale varied from 0 to 5 points. An article with Jadad score ≤ 2 was considered to have low quality. The study was thought to have high quality if Jadad score ≥ 3.[22]

2.4. Statistical analysis

We assessed the risk ratio (RR) with 95% confidence interval (CI) for dichotomous outcomes (complete response, progressive disease, partial response, stable disease, nausea and vomiting, diarrhea, hot flash, and adverse events). Heterogeneity was evaluated using the I^2 statistic, and $I^2 > 50\%$ indicated significant heterogeneity.[23] The random-effects model was used for all meta-analysis. We searched for potential sources of heterogeneity when encountering significant heterogeneity. Sensitivity analysis was performed to detect the influence of a single study on the overall estimate via omitting one study in turn or performing the subgroup analysis. Owing to the limited number (<10) of included studies, publication bias was not assessed. Results were considered as statistically significant for $P < .05$. All statistical analyses were performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

3. Results

3.1. Literature search, study characteristics, and quality assessment

Figure 1 showed the detail flowchart of the search and selection results. Five hundred thirty-eight potentially relevant articles were identified initially. Finally, seven RCTs were included in the meta-analysis.[15–18,24–26]

The baseline characteristics of the included RCTs were shown in Table 1. These studies were published between 2007 and 2016, and the total sample size was 927. The gefitinib was administered at the dose of 250 mg daily, and its combination drugs included anastrozole,[15,17,18] tamoxifen,[16] epirubicin and cyclophosphamide,[24,25] epirubicin and paclitaxel.[26] Jadad scores of the 7 included studies varied from 3 to 5, and all 7 studies had high-quality based on the quality assessment.

3.2. Primary outcomes: complete response and progressive disease

The random-effect model was used for the analysis of primary outcomes. After including four RCTs for the analysis of complete response,[15,17,18,24] the results found that compared to control group for breast cancer, gefitinib supplementation showed no substantial impact on complete response (RR = 1.19; 95% CI = 0.58–2.44; $P = .63$) with no heterogeneity among the studies ($I^2 = 0\%$, heterogeneity $P = .91$, Fig. 2). The meta-analysis of those four RCTs involving 484 patients revealed that gefitinib supplementation demonstrated no obvious effect on progressive disease (RR = 0.81; 95% CI = 0.59–1.11; $P = .18$) compared to control group, and no heterogeneity remained among the studies ($I^2 = 0\%$, heterogeneity $P = .52$, Fig. 3).

3.3. Sensitivity analysis

There was no heterogeneity for the primary outcomes, and thus we did not perform sensitivity analysis via omitting 1 study in turn to detect the heterogeneity.

3.4. Secondary outcomes

In comparison with control intervention for breast cancer, gefitinib supplementation had no remarkable impact on partial response (RR = 0.67; 95% CI = 0.36–1.25; $P = .21$; Fig. 4) or stable disease (RR = 1.02; 95% CI = 0.65–1.60; $P = .92$; Fig. 5) after performing the analysis of 4 RCTs and 484 patients.[15,17,18,24] The meta-analysis of 5 included RCTs[15–18,26] demonstrated similar incidence of nausea and vomiting between 2 groups (RR = 0.99; 95% CI = 0.73–1.33; $P = .93$; Fig. 6). Additionally, gefitinib supplementation was associated with the increase in diarrhea (5 RCTs and 710 patients[15–18,26]; RR = 2.80; 95% CI = 2.23–3.52; $P < .00001$; Fig. 7) and the decrease in hot flash (4 RCTs and 669 patients[15–18]; RR = 0.53; 95% CI = 0.37–0.78; $P = .001$; Fig. 8). The incidence of adverse events in gefitinib supplementation group was higher than that in control group (2 RCTs and 350 patients[16,17]; RR = 1.12; 95% CI = 1.05–1.19; $P = .0006$; Fig. 9).

4. Discussion

Combining endocrine therapy and molecularly targeted agents has emerged as an effective strategy to delay or overcome

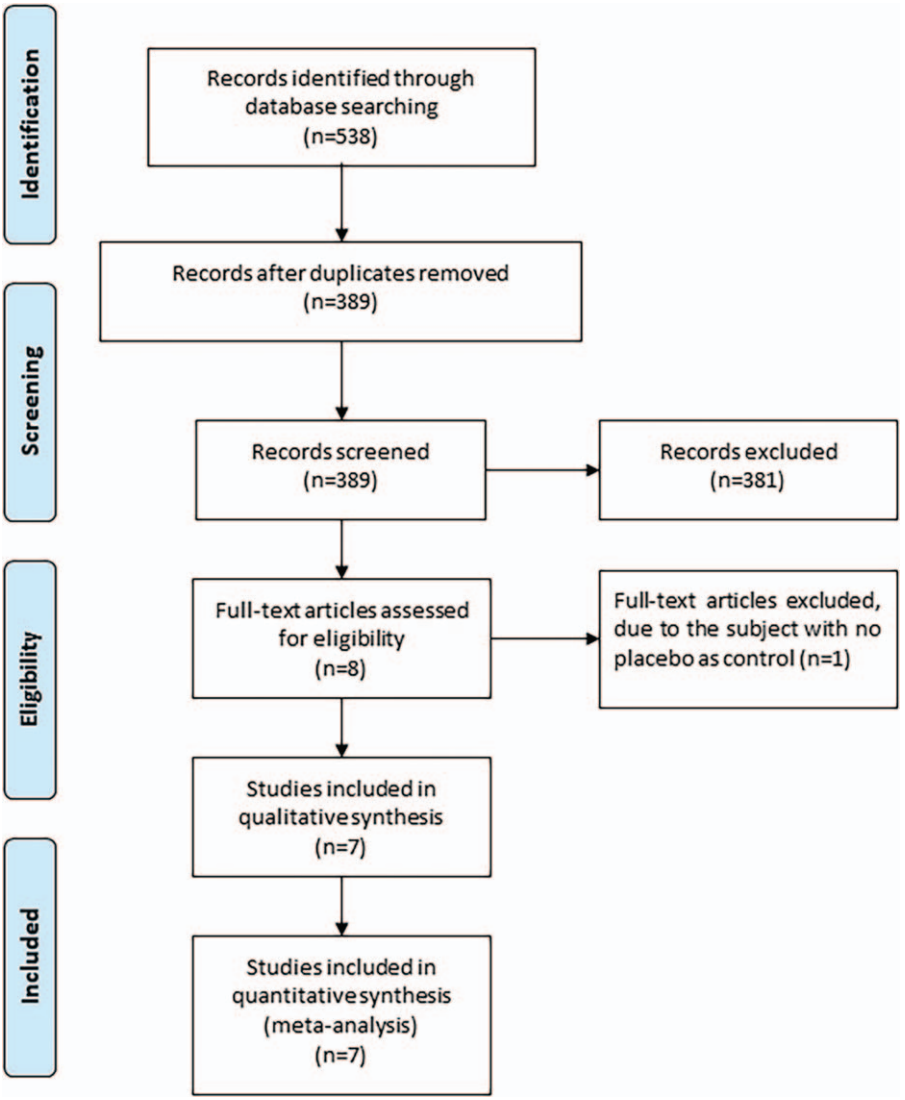

Figure 1. Flow diagram of study searching and selection process.

endocrine resistance in metastatic breast cancer.[27–29] Previous studies reported that the mammalian target of rapamycin and CDK4/6 (Cyclinedependent kinase) inhibition was able to augment the anti-tumor activity of endocrine treatment.[30,31] Several targeted agents improved the outcome of patients with hormone receptor (HR)-positive metastatic breast cancer.[32–34] In addition, gefitinib benefited to the reversal of resistance to estrogen deprivation and fulvestrant in human epidermal EGFR 2 (HER2)-positive and HR-positive breast cancer in the xenograft model.[35]

Several studies reported the efficacy of gefitinib supplementation for breast cancer. In previously untreated postmenopausal women with HR-positive metastatic breast cancer, gefitinib served as the adjunctive therapy to anastrozole and resulted in the improvement in progression-free survival compared to placebo (median progression-free survival, 14.7 vs 8.4 months).[17] One phase II trial assessed the gefitinib combined with tamoxifen in patients with HR-positive metastatic breast cancer, and the results found that gefitinib might enhance the activity of endocrine therapy in specific subsets of endocrine-sensitive patients with the EGFR-dependent resistance.[16]

In contrast, gefitinib was used for the neoadjuvant setting of HR-positive primary breast cancer, and the results revealed no obvious benefit for breast cancer when combined with anastrozole.[9,18] Our meta-analysis found that gefitinib supplementation therapy showed no positive influence on complete response, progressive disease, partial response or stable disease for breast cancer, but revealed the increase in adverse events such as diarrhea.

Several factors may be responsible for these inconsistency and failure to translate preclinical findings into clinical benefit. Firstly, only gefitinib monotherapy results in high response rates in patients with estrogen receptor-positive and tamoxifen-resistant breast cancer,[36] and thus there may be the inverse correlation between the expression of EGFR and estrogen receptor. Secondly, incomplete understanding of molecular mechanisms of endocrine sensitivity may lead to the failure to obtain clinical benefits, and there is little known about the effective inhibition of EGFR signaling. Thirdly, breast cancer patients with previous

Table 1

Characteristics of included studies.

		Gefitinib group						Control group						
No.	Author	Number	Age (yr)	Estrogen receptor (+)	Progesterone receptor (+)	Human epidermal growth factor receptor 2 (+)	Methods	Number	Age (yr)	Estrogen receptor (+)	Progesterone receptor (+)	Human epidermal growth factor receptor 2 (+)	Methods	Jada scores
1	Tryfonidis 2016	36	64.2 (43.5–82.8), median (range)	36	21	0	Anastrozole (1 mg/d) plus gefitinib 250 mg/d for advanced breast cancer	35	63.9 (42.8–84.4), median (range)	35	24	1	Anastrozole (1 mg/d) plus gefitinib placebo	5
2	Osborne 2011	153	61.6 (40–89), mean (range)	151	129	26	Tamoxifen (20 mg/d orally) plus gefitinib (250 mg/d orally) for estrogen receptor-positive metastatic breast cancer	136	63.1 (40–86), mean (range)	134	102	17	Tamoxifen (20 mg/d orally) plus placebo	4
3	Bernsdorf 2011 (1)	94	53±10.2	0	–	78	Four cycles of neoadjuvant epirubicin and cyclophosphamide plus 12 wk of either gefitinib (250 mg daily) or placebo for estrogen receptor negative invasive breast cancer	86	53.1±10.5	0	–	78	Four cycles of neoadjuvant epirubicin and cyclophosphamide plus placebo	4
4	Bernsdorf 2011 (2)	59	52.8±10.1	–	–	58	Four cycles of epirubicin and cyclophosphamide plus 12 wk of daily treatment with gefitinib (250 mg) for estrogen receptor negative breast cancer	56	53.3±10.5	–	–	56	Four cycles of epirubicin and cyclophosphamide plus placebo	3
5	Cristofanilli 2010	43	61 (41–82), median (range)	38	36	–	Anastrozole 1 mg/d and gefitinib 250 mg/d orally for hormone receptor–positive metastatic breast cancer	50	58 (37–84), median (range)	41	30	–	Anastrozole 1 mg/d and placebo orally	3
6	Guarneri 2008	32	46.5 (33–69), median (range)	64	42	31	Epirubicin 90 mg/sqm and paclitaxel 175 mg/sqm on day 1 plus gefitinib 250 mg daily for operable breast cancer	31	51 (31–66), median (range)	72	60	10	Epirubicin 90 mg/sqm and paclitaxel 175 mg/sqm on day 1 plus placebo	3
7	Smith 2007	31	69.8	97	61	–	Anastrozole 1 mg daily and gefitinib 250 mg/d orally for hormone receptor–positive early breast cancer	85	70.2	100	73	–	Anastrozole 1 mg daily and placebo	4

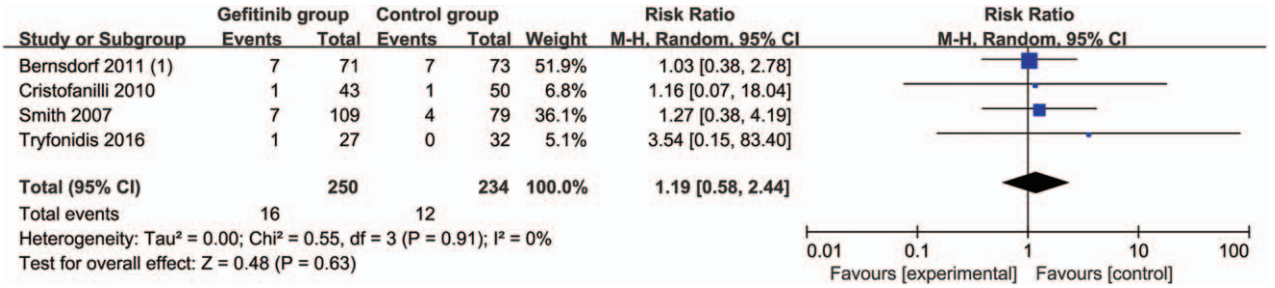

Figure 2. Forest plot for the meta-analysis of complete response.

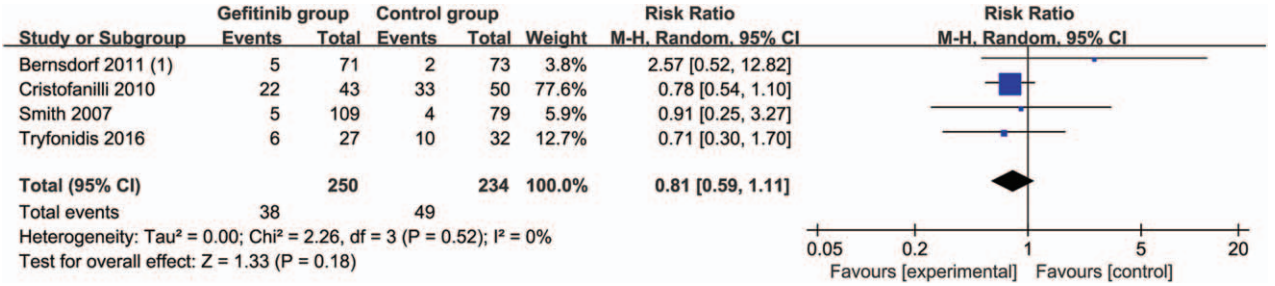

Figure 3. Forest plot for the meta-analysis of progressive disease.

exposure to adjuvant endocrine therapy may reduce the efficacy of gefitinib supplementation.

Several limitations existed in this meta-analysis. Firstly, our analysis was based on only seven RCTs, and more RCTs with large sample size should be conducted to explore this issue. Secondly, different combination drugs with gefitinib were applied for breast cancer in the included RCTs, which may produce some effect on the pooling results. Thirdly, different cancer subtypes such as HR–positive and negative breast cancer patients were included in this meta-analysis and may produce some heterogeneity, but current limited data was insufficient for performing the subgroup analysis of cancer subtype. Fourthly, the approval of the committee on research ethics and informed consent were very crucial for the RCTs,[37,38] but some included RCT did not report whether the committee on research ethics approved the study and whether informed consent was obtained.[15,17,18]

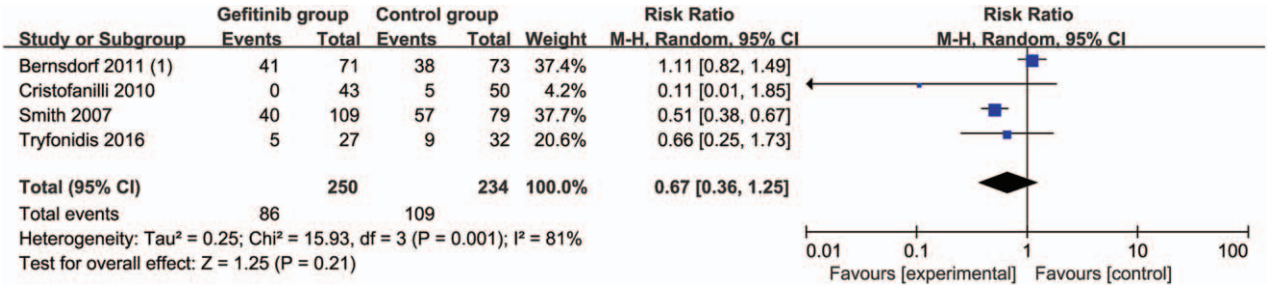

Figure 4. Forest plot for the meta-analysis of partial response.

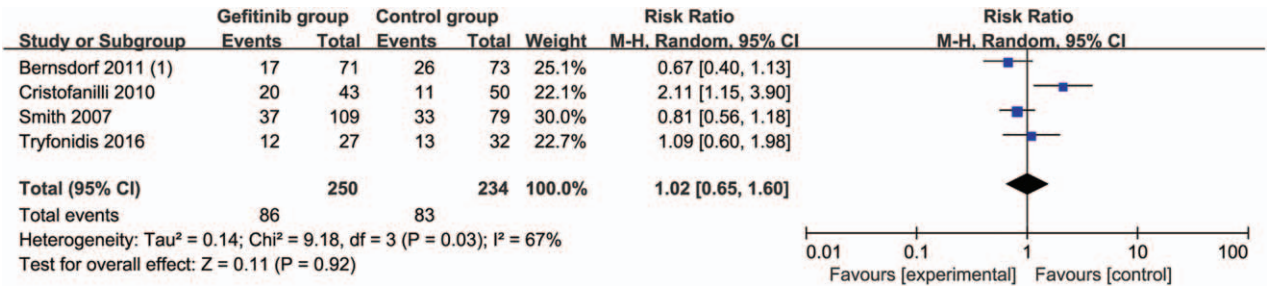

Figure 5. Forest plot for the meta-analysis of stable disease.

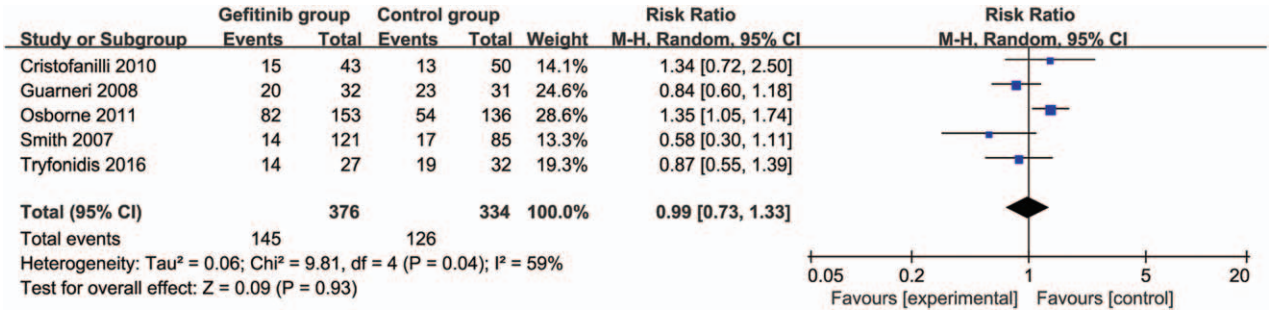

Figure 6. Forest plot for the meta-analysis of nausea and vomiting.

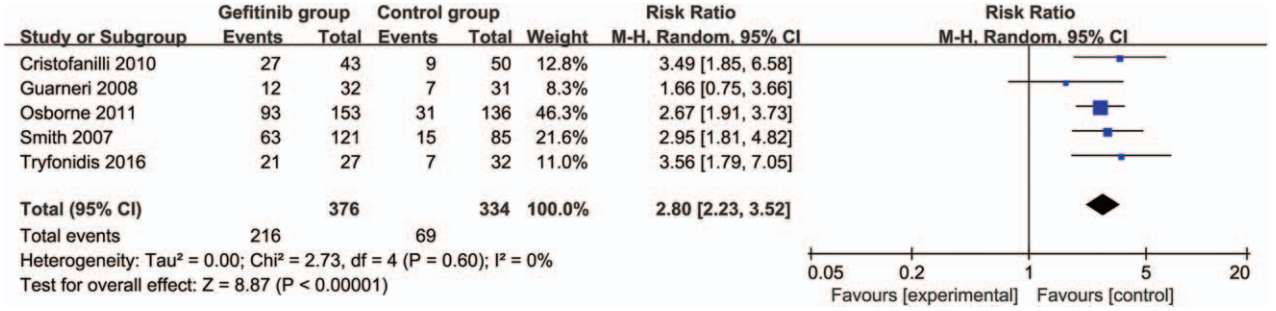

Figure 7. Forest plot for the meta-analysis of diarrhea.

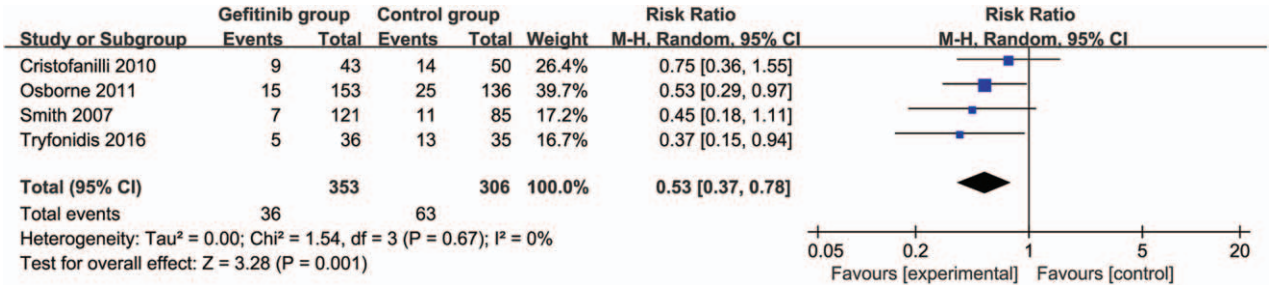

Figure 8. Forest plot for the meta-analysis of hot flash.

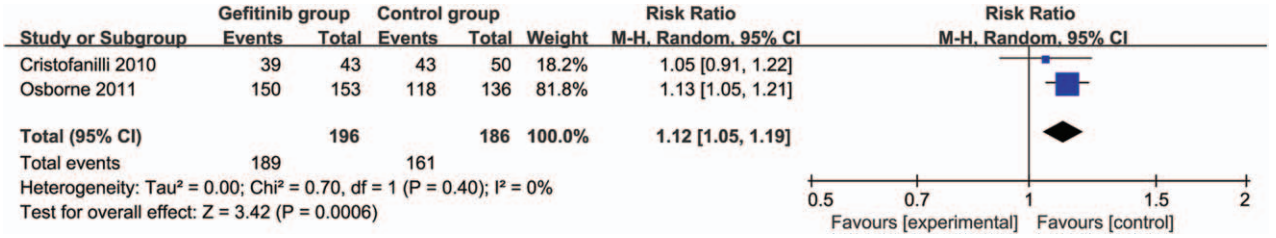

Figure 9. Forest plot for the meta-analysis of adverse events.

5. Conclusion

Gefitinib supplementation may show no obvious benefits in patients with breast cancer with regard to complete response, progressive disease, partial response or stable disease, and more studies should be conducted to confirm this issue.

Author contributions

Methodology: Tian Tian.
Writing – original draft: Jing Ye.
Writing – review & editing: Tian Tian.

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