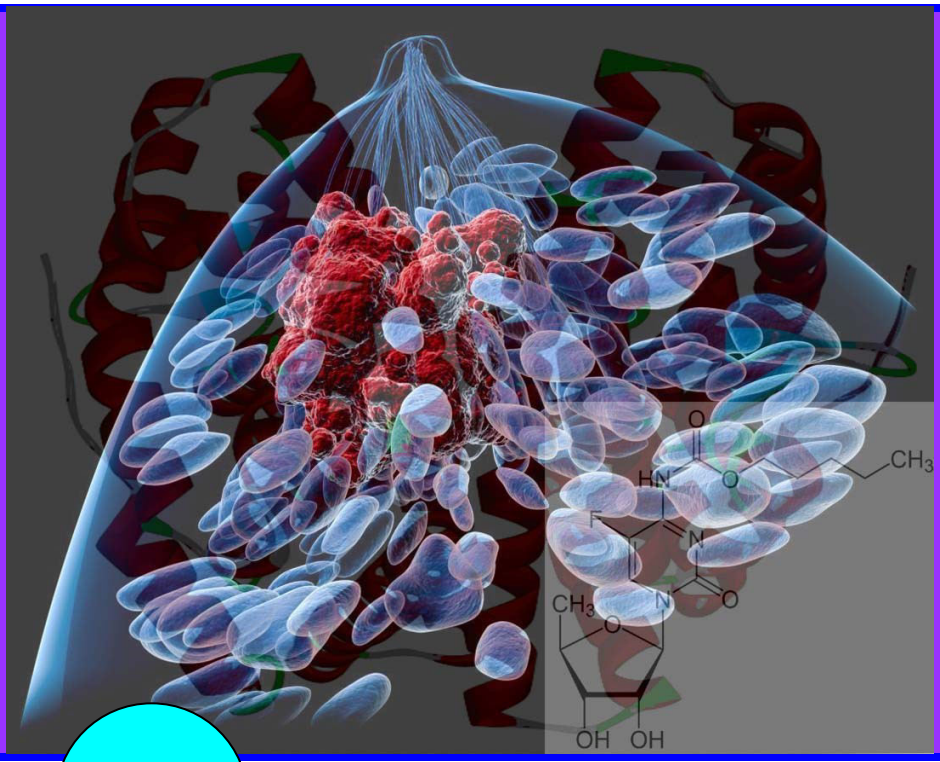

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Meta-analysis

Effect of capecitabine on breast cancer patients with different estrogen receptor status

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Abstract

This meta-analysis is to compare the efficacy of capecitabine versus non-capecitabine chemotherapy on breast cancer patients with different estrogen receptor status. We searched relevant literature from the EMBASE, PubMed and OVID library to analyze the pathologic complete response (PCR) rate, overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), and time to disease progression (TTP). Eleven different studies were enrolled, which revealed that estrogen receptor positive breast cancer patients who received treatment regimen containing capecitabine can effectively improve PFS, PCR, TTP. However, the difference between capecitabine-containing and non-capecitabine groups had no significant effect for DFS and OS. Estrogen receptor negative breast cancer patients who received treatment regimen containing capecitabine could improve DFS and TTP. However, there was no significant effect for PFS, PCR and OS. The results indicated that capecitabine in combination with other chemotherapy drugs for breast cancer is effective, which can delay the progression time in patients to some extent.

Introduction

The incidence of breast cancer increases with age, which has become the second leading cause of cancer death in women (Tang et al., 2016). Breast cancer molecular typing has gained international attention for therapy purpose. The concept of molecular portraits of breast cancer was classified into two subtypes: estrogen receptor positive and estrogen receptor negative breast cancer (Perou et al., 2000). In the 12th St. Gallen International Breast Cancer Conference, a new approach to the classification of breast cancer patients according to intrinsic biological subtypes has been adopted by an expert panel.

Capecitabine is used for treating progressive and metastatic breast cancer, which is concerted to 5-fluorouracil selectively in tumors via a cascade of three enzymes (Miwa et al., 1998). In addition, high expression profile of thymidine phosphorylase in breast cancer cells accounts for the superior efficacy of capecitabine treatment in breast cancer. The previous foreign studies indicated that the effective rate of capecitabine monotherapy or combination therapy with other drugs ranged from 28 to 75% (O'Shaughnessy et al., 2010; Tan et al., 2012). Another study found that cytotoxic drugs such as texol and texotere simultaneously increased the thymidine phosphorylase activity, which might result in improving the efficacy of capecitabine (Sawada et al., 1998).

Researches have shown that either capecitabine

monotherapy or combined with cytotoxic drug or targeted drugs presented different clinical benefit rates and efficiency (Lee et al., 2008; von Minckwitz et al., 2010; Bear et al., 2012). The efficacy of capecitabine therapy for heavily pretreated metastatic breast cancer patients had an association with estrogen receptor status (Osako et al., 2009). Advanced breast cancer patient with estrogen receptor positive status responses better to capecitabine therapy (Siva et al., 2008). In this study, we classified the research object according to estrogen receptor status to determine whether there were differences in the efficacy under capecitabine treatment. Information obtained from this paper can help to suggest patients selecting capecitabine-containing chemotherapy drugs based on the status of the estrogen receptor.

Materials and Methods

Inclusion criteria

Inclusion criteria for this meta-analysis were as follows: a) hormone receptor status had been evaluated in pathologically confirmed breast cancer patients; b) comparison of capecitabine-containing therapy with non-capecitabine therapy; c) sufficient information provided to analyze pathologic complete response (PCR) rate, overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), and time to disease progression (TTP); d) retrospective or prospective studies.

Exclusion criteria

Studies meeting the following one criterion were excluded: a) study objects without clear diagnosis or inclusion and exclusion criteria; b) study objects without hormone receptor status; and c) studies had no sufficient data.

Search strategy

We conducted a systematic search in the Pubmed, EMBASE, and OVID databases, using the MeSH terms and free keywords "breast cancer" combined with "capecitabine", from their dates of inception to November 1, 2016, and identified all potentially relevant articles, language restrictions were not employed. We also searched the reference lists of the full-text papers and reviewed studies from all of the relevant publications to identify any omitted studies.

Data extraction and statistical analysis

A self-designed data extraction form was used to extract information including first author, year of publication, characteristics of the study population, study design, outcome measures. The literature screening, quality assessment and data extraction were carried out by two reviewers. In case of disagreement, a third investigator would help to resolve the discrepancies Stata 13.1 software was used for statistical analysis. Relative risk (RR) and 95% CI were used to assess the binary data value in this meta-analysis. The statistical heterogeneity among the various studies was assessed by the Chi-squared study and its associated I^2 value. The fixed-effects model was applied to merge the included studies for further analysis if no significant heterogeneity was detected ($p>0.1$, $I^2 \leq 50\%$), whereas the trials were sub-grouped according to the medicine used to analyze the sources of clinical heterogeneity if the heterogeneity was significant ($p \leq 0.1$, $I^2 > 50\%$). Egger's test was used for estimating a possible publication bias.

Results

Literature search results

A total of 2,197 literature were retrieved. After deduplication, preliminary screening and intensive reading, eleven literature were finally included after intensive reading of the text (Figure 1).

Quality assessment and publish bias

A summary of quality evaluation results for included studies is presented in Figure 2 and Figure 3. Because of the nature of the interventions, most studies have high-risk of blinding of participants and intervention providers. There are 4 studies reference to randomization used computer-generated random sequence and a block -design randomization procedure, while other studies no description of how to carry out randomization. 3 trials allocated patients treatment were not masked and 5 trials had comparable baselines. Blinded data analysis independent of the trial in all studies. Most of the trial reports were not complete and not selective. Overall, the studies enrolled in this meta-analysis had moderate quality. Egger's test obtained $p=0.245$, indicated there was no obvious publication bias.

Basic information of the included literature

The basic information of all the included studies is shown in Table I, which mainly included first author, year of publication, follow-up time, median follow-up period, basic characteristics of the study object, chemotherapy program, study group and control group population, and outcome measures.

Analysis of capecitabine treatment for ER+ breast cancer vs. ER- breast cancer

Eleven literature were included (Lee et al., 2008; O'Shaughnessy et al., 2010; Joensuu et al., 2012; Zambetti et al., 2012; Glück et al., 2013; Gligorov et al., 2014; Twelves et al., 2014; Martin et al., 2015; Shankar et al., 2015; Twelves et al., 2016; Zielinski et al., 2016). Interventions in the study group consisted of capecitabine treatment, while interventions in the control group that

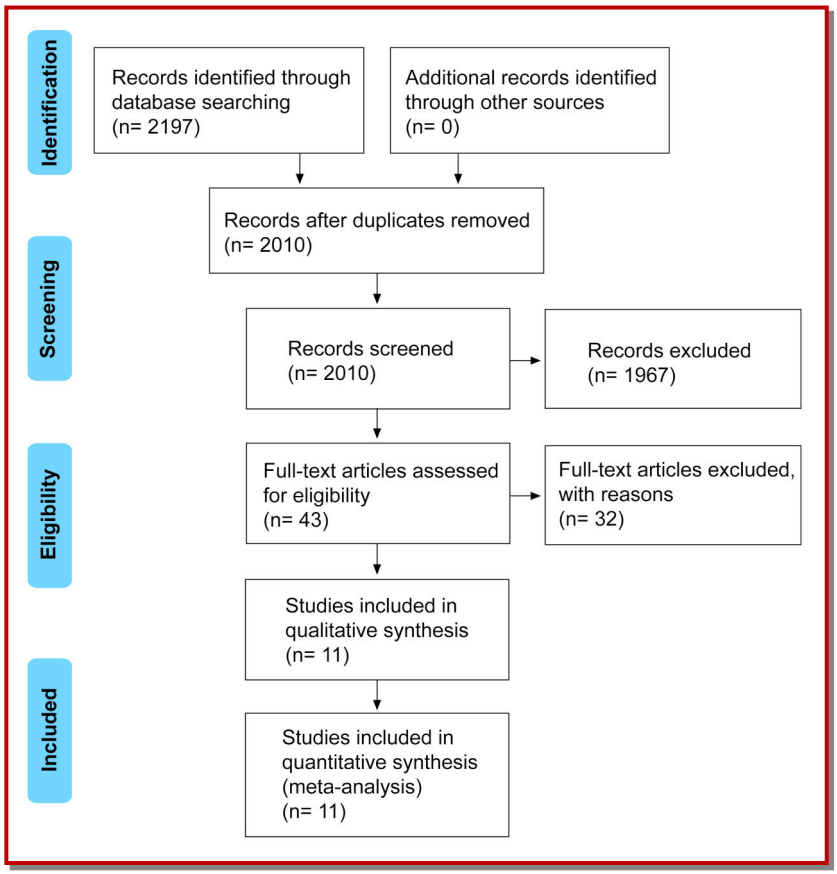

Figure 1: Preliminary screening and intensive reading of literatures finally included

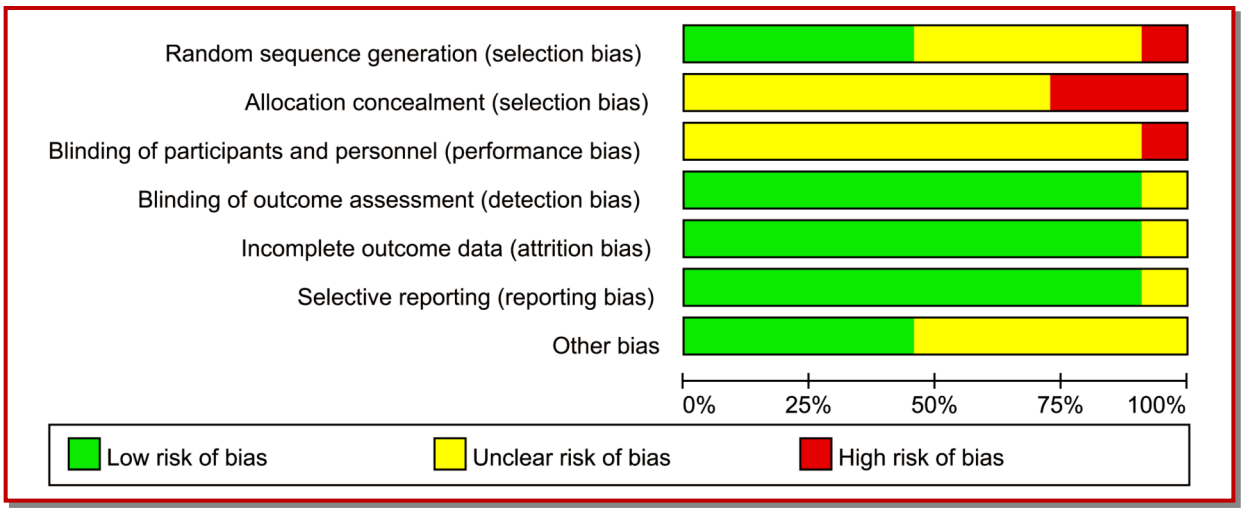

Figure 2: Quality evaluation results for included studies

did not contain capecitabine. In ER+ breast cancer trials, there were five outcome measures which included PFS, PCR, DFS, OS, and TTP. PFS [RR= 0.93, 95% CI (0.88-0.97)] (Figure 4A), PCR [RR= 0.24, 95% CI (0.09-0.63)] (Figure 4B), and TTP [RR= 0.62, 95% CI (0.46-0.84)] were reported in four (Gligorov et al., 2014; Twelves et al., 2014; Shankar et al., 2015; Twelves et al., 2016), two (Lee et al., 2008; Zambetti et al., 2012), and one (Zambetti et al., 2012) studies respectively that presented significantly difference between the study group and control group. When the outcome measures were, three studies have reported the results of DFS [RR= 0.89, 95% CI (0.71-1.12)] (O'Shaughnessy et al., 2010; Joensuu et al., 2012; Martin et al., 2015) and OS [RR= 0.89, 95% CI (0.74-1.07)] (Glück et al., 2013; Gligorov et al., 2014; Zielinski et al., 2016) that revealed that the difference

Table I

Basic information of included studies

References	Follow-up duration	Median follow-up duration (months)	Patients' Characters	Treatment regimens	Number of patients in each group				Outcomes
					ER+	ER+	ER-	ER-	
					Study group	Control group	Study group	Control group	
Martín et al., 2015		79.2	Women age 18 to 70 years with a histologic diagnosis of invasive human epidermal growth factor receptor 2 (HER2)–positive breast cancer with axillary involvement (T1-3/N1-3).	Epirubicin plus cyclophosphamide (EC; 90 and 600 mg/m^2, respectively, four cycles), followed by docetaxel (100 mg/m^2; four cycles; EC-T) as control group; epirubicin plus docetaxel (ET; 90 and 75 mg/m^2, respectively, four cycles), followed by capecitabine (1,250 mg/m^2 twice a day on days 1 to 14, four cycles; ET-X) as treatment group; all regimens were given every 3 weeks	39	50	26	27	DFS
Zielinski et al., 2016	2008-2014	54.3	Patients aged 18 years or older who had an Eastern Cooperative Oncology Group performance status 0–2 and measurable or non-measurable HER2-negative locally recurrent or metastatic breast cancer who had received no previous chemotherapy for locally recurrent or metastatic breast cancer.	Bevacizumab plus paclitaxel (bevacizumab 10 mg/kg on days 1 and 15 plus paclitaxel 90 mg/m^2 on days 1,8, and 15 every 4 weeks) as control group; bevacizumab plus capecitabine (bevacizumab 15 mg/kg on day 1 plus capecitabine 1000 mg/m^2 twice daily on days 1–14 every 3 weeks) as treatment group.	201	205	64	60	OS
Twelves et al., 2016	*	*	Women aged 18 years or older who had locally advanced or metastatic breast cancer, 3 prior chemotherapy regimens (including 2 for advanced and/or metastatic disease), including an anthracycline and a taxane. HER2-targeted therapy was not allowed during study treatment.	Intravenous eribulin mesylate 1.4 mg/m^2 on days 1 and 8 as control group; twice-daily oral capecitabine 1250 mg/m^2 on days 1–14 (21-day cycles) as treatment group.	278	259	216	233	PFS
Twelves et al., 2014	*	*	Women with locally recurrent or metastatic breast cancer had received between two and five previous chemotherapy regimens (including an anthracycline and a taxane), two or more of which were for locally recurrent or metastatic disease.	Intravenous eribulin mesylate 1.4 mg/m^2 on days 1 and 8 as control group; twice-daily oral capecitabine 1250 mg/m^2 on days 1–14 (21-day cycles) as treatment group.	449	595	288	376	PFS

Table I (Cont.)

Basic information of included studies

References	Follow-up duration	Median follow-up duration (months)	Patients' Characters	Treatment regimens	Number of patients in each group				Outcomes
					ER+ Study group	ER+ Control group	ER- Study group	ER- Control group	
Shankar et al., 2015	2005-2010	38	Patients aged range from 40-72 years with hormone receptor positive metastatic breast cancer.	Combination of an aromatase inhibitor (AI) and capecitabine as treatment group; aromatase inhibitor (AI) as control group. Capecitabine 650 mg/m² on days 1–14 (21-day cycles)	31	22			PFS
Joensuu et al., 2012	2004-2010	59	Women age 18 to 65 years had histologically confirmed invasive breast cancer with regional lymph nodes containing cancer or node-negative cancer with primary tumor diameter greater than 20 mm and negative progesterone receptor expression in immunohistochemistry	Docetaxel plus capecitabine +cyclophosphamide epirubicin and capecitabine as treatment group; docetaxel+ cyclophosphamide, epirubicin and fluorouracil as control group. Capecitabine 900 mg/m² twice a day, days 1–15, every 3 weeks	580	562	171	183	DFS
Gligorov et al., 2014	2009-2011	11.9	Women aged 18 years or older with HER2-negative metastatic breast cancer with at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors; having an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or 0; a life expectancy of at least 12 weeks.	Bevacizumab and capecitabine as treatment group; Bevacizumab only as control group. Capecitabine 1000 mg/m² twice per day on days 1–14, every 3 weeks.	64	69	27	25	PFS OS
Lee et al., 2008	*	37	Patients had to be aged 18 years or older with an Eastern Co-operative Oncology Group (ECOG) performance status ≤1 and have biopsy-proven, newly diagnosed stage II/III breast cancer with axillary lymph node involvement.	Docetaxel and capecitabine as treatment group; doxorubicin and cyclophosphamide as control group. Capecitabine 1,000 mg/m² orally twice daily on days 1–14 every 3 weeks for four cycles.	64	62	39	39	PCR
Glück et al., 2013	*	ER+ (C+D) 48.4 ER+ (D) 43.6 ER- (C+D) 23.9 ER- (D) 21.5	Patients were aged 18 years with histologically orcytologically confirmed unresectable metastatic breast cancer that had recurred following anthracycline treatment in the (neo)adjuvant setting. Patients were required to have a Karnofsky performance score 70% and life expectancy 3 months.	Capecitabine and docetaxel(C+D) as treatment group; docetaxel(D) as control group. Capecitabine 1250 mg/m² twice daily, days 1-14, 21-day cycles.	90	95	88	83	OS TTP

Table I (Cont.)

Basic information of included studies									
References	Follow-up duration	Median follow-up duration (months)	Patients' Characters	Treatment regimens	Number of patients in each group				Outcomes
					ER+ Study group	ER+ Control group	ER- Study group	ER- Control group	
Zambetti et al., 2012	2004-2009	*	Patients had to be females ≥18 years old, presenting for the first time with unilateral, operable, invasive breast cancer > 2.0 cm in diameter, with no previous treatment for invasive malignancy, and an Eastern Cooperative Oncology Group (ECOG) performance status ≤1. Sufficient tissue for receptor status and translational studies was mandatory.	Doxorubicin and paclitaxel + Cyclophosphamid, methotrexate and capecitabine as treatment group; doxorubicin and paclitaxel +Cyclophosphamid, methotrexate and fluorouracil as control group. 1850 mg/m² oral capecitabine divided into two daily doses from day 1 to 14) at 4-week intervals	61	60	42	43	PCR
OShaughnessy et al., 2010	*	60	Patients aged 18-70 years, with breast cancer as ≥1 positive lymph node, T1-3, and M0; or node negative with tumors >2 cm and M0; or node negative with tumors >1 cm.	Doxorubicin plus cyclophosphamide followed by docetaxel with capecitabine as treatment group; doxorubicin plus cyclophosphamide followed by docetaxel without capecitabine as control group.	*	*	*	*	DFS

between the study group and control group was not statistically significant, as shown in Figure 4C and Figure 5A.

In the ER- breast cancer, there were also five outcome measures: PFS, PCR, DFS, OS, and TTP. When the outcomes were PFS [RR= 0.96, 95% CI (0.91-1.02)], PCR [RR= 1.09, 95% CI (0.73-1.63)], and OS [RR= 0.94, 95% CI (0.72-1.22)], three (Gligorov et al., 2014; Twelves et al., 2014; Twelves et al., 2016), two (Lee et al., 2008; Zambetti et al., 2012), and three (Glück et al., 2013; Gligorov et al., 2014; Zielinski et al., 2016) studies were included respectively. Results showed that the difference between study group and control group was not statistically significant, as shown in Figure 5B, Figure 6A and Figure 6B. Whereas, the obvious difference between study group and control group of DFS [RR= 0.74, 95% CI (0.58-0.95)] (Figure 5C) and TTP [RR= 0.73, 95% CI (0.53-0.98)] had been confirmed using meta-analysis of three (Joensuu et al., 2012; Glück et al., 2013; Martin et al., 2015) and one (Glück et al., 2013) included studies respectively. The summary of the results of all outcome measures is shown in Table II.

Discussion

Breast cancer is a common malignant tumor that has a strong heterogeneity of clinical presentation, histological and molecular typing in the female worldwide. Diagnosis by estrogen-receptor status subtype added significant prognostic and predictive information for breast cancer (Parker et al., 2009). Capecitabine monotherapy for locally advanced or metastatic breast cancer had different overall response rate and progression-free survival in patients with different hormone-receptor status (Osako et al., 2009). The results of this study indicated that ER+ breast cancer patients receiving capecitabine containing treatment regimens could significantly improve PFS, PCR and TTP. Whereas the difference in DFS and OS between study and control groups was not significant. ER- breast cancer patients receiving capecitabine contain-ing treatment regimens could improve DFS and TTP, while the comparison of PFS, PCR and OS had no statistical difference. In contrast to patients with ER- disease, those with ER+ tumors seemed to benefit from the capecitabine treatment regimens, suggesting capecitabine-containing chemotherapy regimens have different treatment effects by ER status.

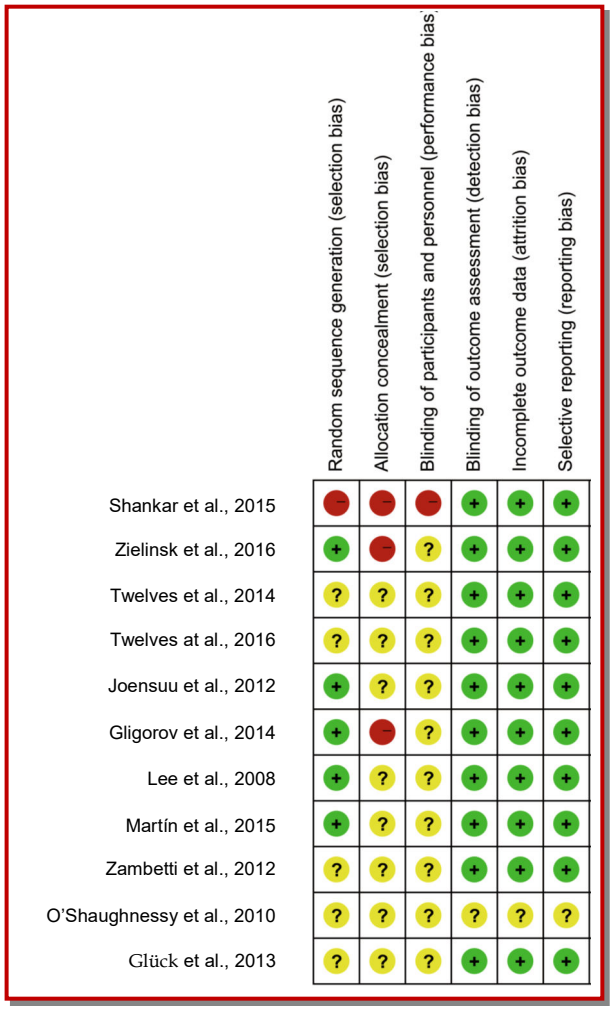

Figure 3: Risk of bias summary

The reasons for the different results obtained in ER+ or ER- studies may relate to the patient populations enrolled, the patients in the meta-analysis included node-positive early breast cancer and advan-ced or metastatic breast cancer. The National Compre-hensive Cancer Network (NCCN) guideline for early breast cancer patients recommends treatment with anthracycline and/or taxane chemotherapy which contained no capecitabine. And the capecitabine dosing regimen recommended by NCCN is 1000–1250 mg/m^2 twice daily, but several studies included in our meta-analysis reduced this by 10 to 35%. Finally, capecitabine -based chemotherapy resulted in increasing in adverse effects, which may have led to reduced compliance with therapy.

The main limitation of this study is that the included original studies were very few. And the number of studies for each outcome measure was less than four, which resulting in a big bias to influence the authen-ticity of effect. Further randomized controlled trials of capecitabine therapy on targeted populations with the adjuvant and neoadjuvant setting.

Conclusion

Capecitabine in combination with other chemotherapy drugs for breast cancer is effective, which can delay the progression time in patients to some extent. Compared with ER-breast cancer, the curative effect of capecita-bine-containing chemotherapy regimen is more obvious in ER+ breast cancer patients. Whether there is an additional capecitabine treatment benefit in ER positive and ER negative breast cancer requires further evalua-tion because of potential bias.

Table II

Summary of outcome measures in the included studies

Outcome measures	Number of studies	Included studies	ER+ RR and 95%RR	ER- RR and 95%RR
PFS	4 (ER+)	Twelves et al., 2016	0.93 (0.88-0.97)	0.96 (0.91-1.02)
	3 (ER-)	Twelves et al., 2014		
PFS	4 (ER+)	Shankar et al., 2015	0.93 (0.88-0.97)	0.96 (0.91-1.02)
	3 (ER-)	Gligorov et al., 2014		
PCR	2	Lee et al., 2008	0.24 (0.09-0.63)	1.09 (0.73-1.63)
PCR	2	Zambetti et al., 2012	0.24 (0.09-0.63)	1.09 (0.73-1.63)
DFS	3	Martín et al., 2015	0.89 (0.71-1.12)	0.74 (0.58-0.95)
		Joensuu et al., 2012		
		O'Shaughnessy et al., 2010		
OS	3	Zielinski et al., 2016	0.89 (0.74-1.07)	0.94 (0.72-1.22)
		Gligorov et al., 2014		
		Glück et al., 2013		
TTP	1	Glück et al., 2013	0.62 (0.46-0.84)	0.73 (0.53-0.98)

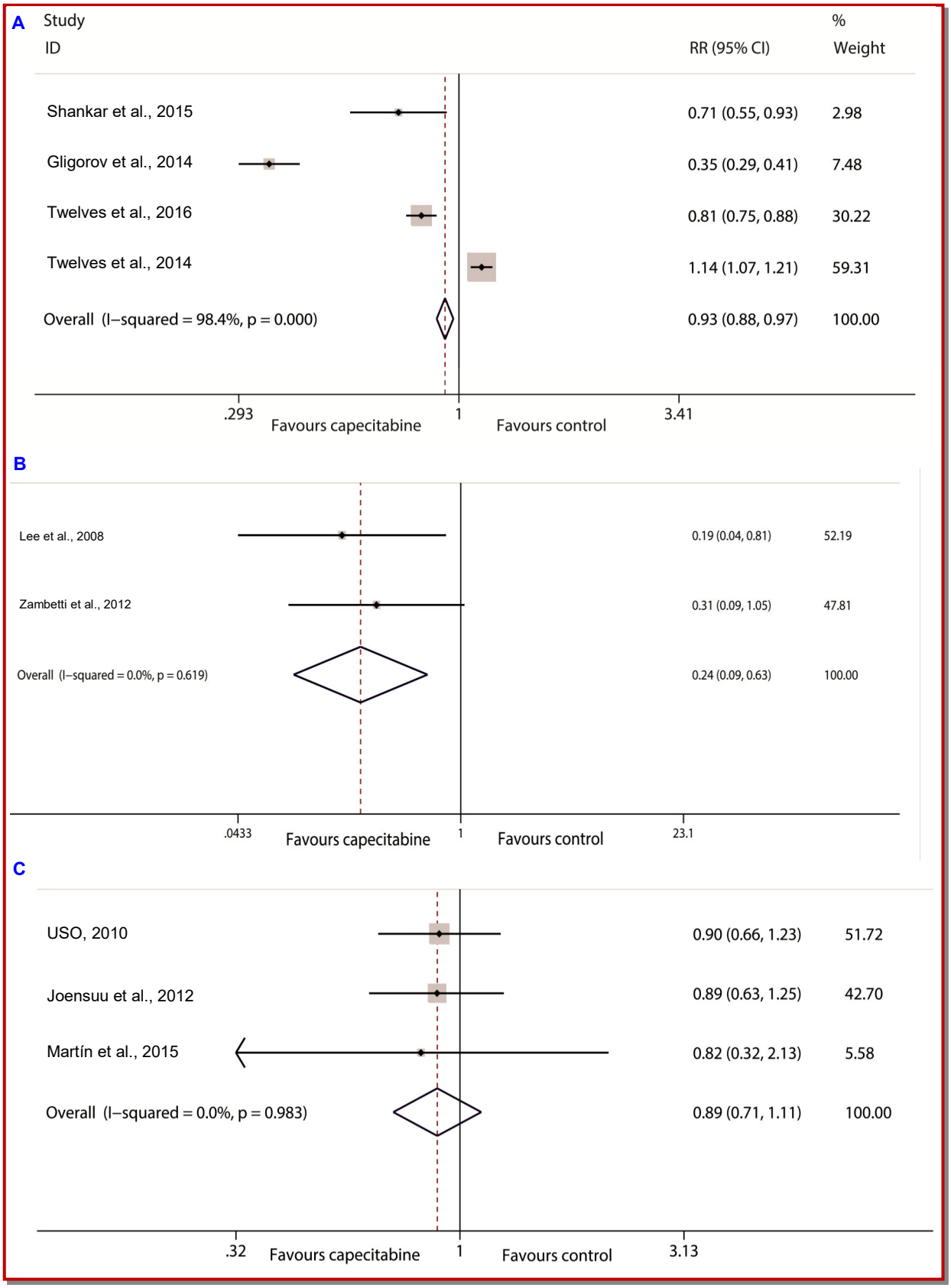

Figure 4: ER+ breast cancer PFS analysis of different comparison groups (A); ER+ breast cancer PCR analysis of different comparison groups (B); ER+ breast cancer DFS analysis of different comparison groups (C)

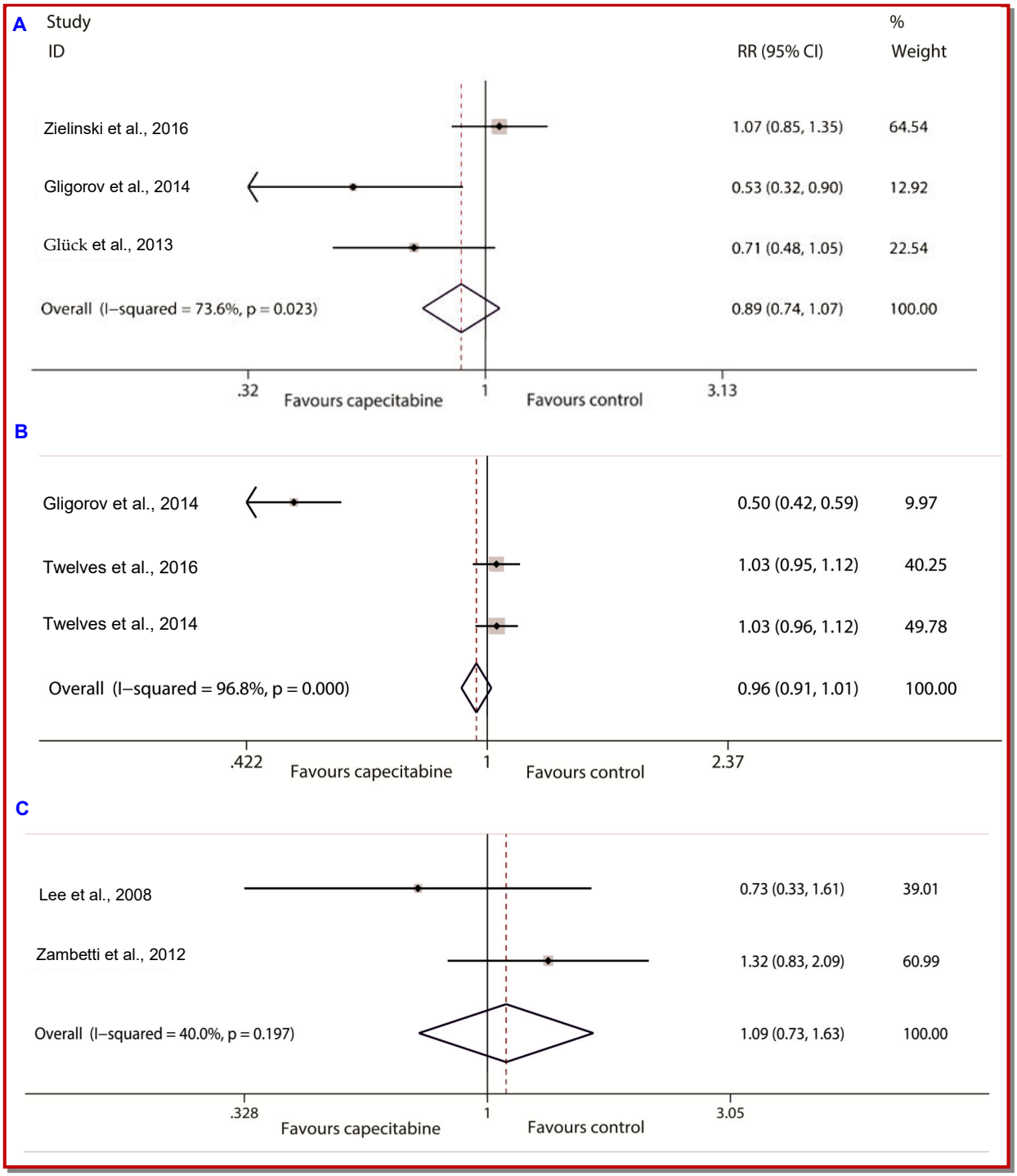

Figure 5: ER+ breast cancer OS analysis of different comparison groups (A); ER- breast cancer PFS analysis of different comparison groups (B); ER- breast cancer DFS analysis of different comparison groups (C)

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Conflict of Interest

Authors declare no conflict of interest.

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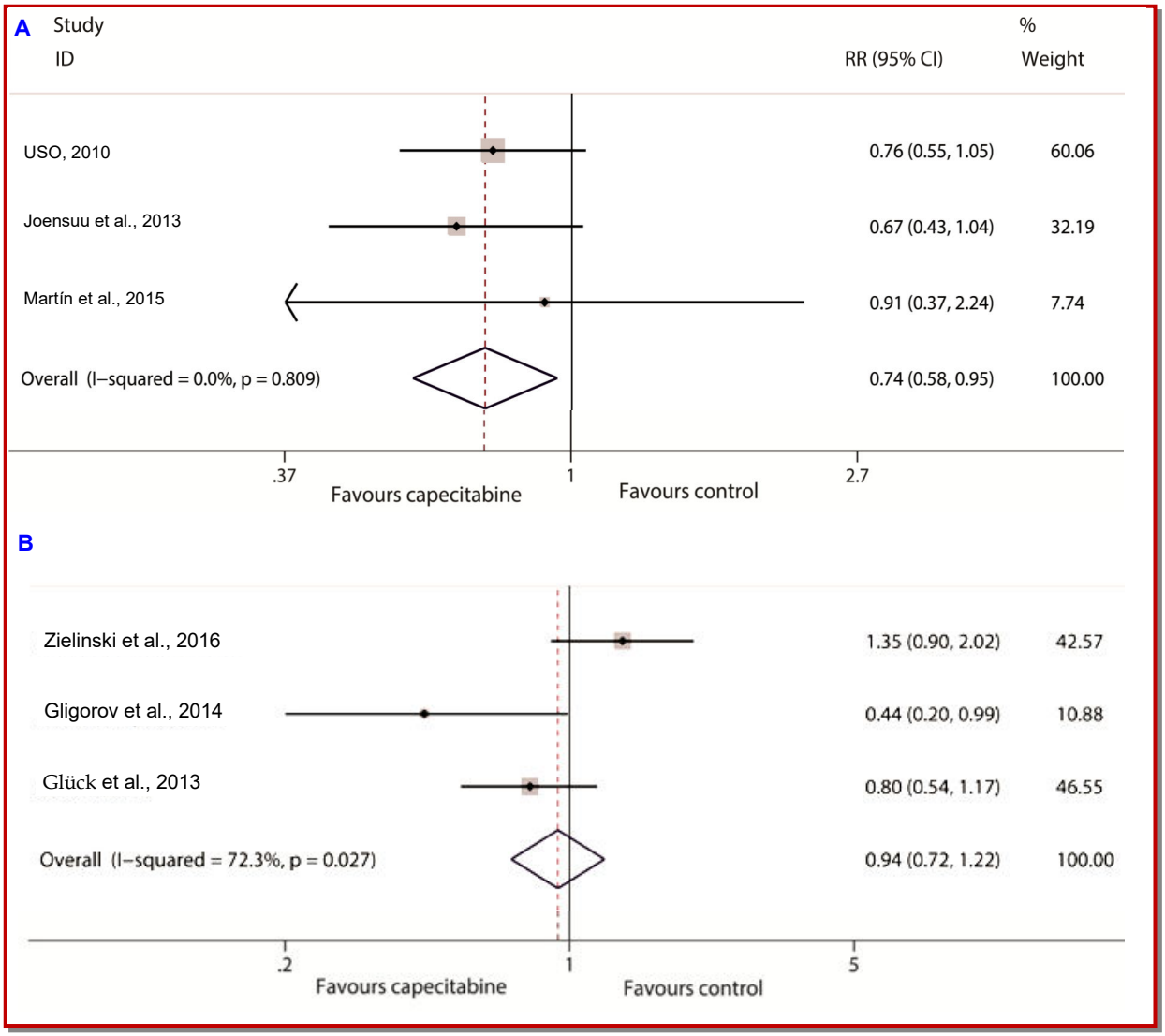

Figure 6: ER- breast cancer PCR analysis of different comparison groups (A); ER- breast cancer OS analysis of different comparison groups (B)

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