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CLINICAL TRIAL

What lies behind chemotherapy-induced amenorrhea for breast cancer patients: a meta-analysis

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Abstract To evaluate the incidence of chemotherapy-induced amenorrhea (CIA) and its therapeutic impact in premenopausal breast cancer patients. A systematic search was performed to identify clinical studies that compared the incidence of CIA with different chemotherapy regimens and oncological outcomes with and without CIA. The fixed-effects and random-effects models were used to assess the pooled estimates. Heterogeneity and sensitivity analyses were performed to explore heterogeneity among studies and to assess the effects of study quality. A total of 15,916 premenopausal breast cancer patients from 46 studies were included. The cyclophosphamide-based regimens, taxane-based regimens, and anthracycline/epirubicin-based regimens all increased the incidence of CIA with pooled odds ratios of 2.25 (95 % CI 1.26–4.03, $P = 0.006$), 1.26 (95 % CI 1.11–1.43, $P = 0.0003$) and 1.39 (95 % CI 1.15–1.70, $P = 0.0008$), respectively. The three-drug combination regimens of cyclophosphamide,anthracycline/epirubicin, and taxanes (CAT/CET) caused the highest rate of CIA compared with the other three drug combinations (OR 1.41, 95 % CI 1.16–1.73, $P = 0.0008$). Tamoxifen therapy was also correlated with a higher incidence of CIA, with an OR of 1.48. Patients with CIA were found to exhibit better disease-free survival (DFS) and overall survival (OS) compared with patients without CIA. With respect to molecular subtype, this DFS advantage remained significant in hormone-sensitive patients (HR 0.61, 95 % CI 0.52–0.72, $P < 0.00001$). The current meta-analysis has demonstrated that anthracycline/epirubicin, taxanes, cyclophosphamide, and tamoxifen all contributed to elevated rates of CIA, and CIA was not merely a side effect of chemotherapy but was a better prognostic marker, particularly for ER-positive premenopausal early-stage breast cancer patients. However, this topic merits further randomized control studies to detect the associations between CIA and patient prognosis after adjusting for age, ER status, and other influential factors.

Keywords Breast cancer · Chemotherapy-induced amenorrhea · Incidence · Prognosis · Meta-analysis

Introduction

Breast cancer is the most common cancer among women in Western countries, with an estimated 226,870 new cases each year and 39,510 cancer deaths per year [1]. Among the newly diagnosed cancers, 7 % occur in women younger than 40 years old, and 25 % occur in premenopausal women [2]. Chemotherapy can prolong overall survival (OS) and is an important standard systemic treatment for most breast cancer patients, particularly for premenopausal young women. Therefore, as a consequence of chemotherapy, women who are premenopausal will develop transient chemotherapy-induced amenorrhea (CIA). As the EBCTCG overview provides evidence of improved prognosis among breast cancer patients younger than 50 years after ovarian ablation or adjuvant chemotherapy (independently) [3, 4], the significance of CIA is under discussion.

Jianli Zhao, Jieqiong Liu, and Kai Chen contributed equally to this study.

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The incidence of CIA is associated with the type, duration, schedule, and dosage of chemotherapy and is age related. However, doubts remain concerning the impact of each single-agent chemotherapy and combination regimen on amenorrhea, such as the effect of taxane-based regimens on amenorrhea. Martin reported higher rates of amenorrhea with six cycles of docetaxel, doxorubicin, and cyclophosphamide (TAC) compared with six cycles of fluorouracil, doxorubicin, and cyclophosphamide ($P = 0.007$) [5], whereas Davis's study indicated that CIA rates may decrease with the addition of taxanes [6]. The effect of tamoxifen on the incidence of CIA is controversial. Some studies have reported that tamoxifen increases CIA [7], whereas other studies have demonstrated no impact by tamoxifen [8, 9]. In most clinical trials, CIA has been found to be predictive of improved outcomes for breast cancer patients [10, 11], but CIA causes some physical and psychological side effects, such as sexual dysfunction and menopausal symptoms [12]. Therefore, considering the negative influence of CIA on quality of life as well as the potential confounding factors of age or chemotherapy regimens on prognosis, it is important for breast cancer oncologists to seriously consider the prognostic role of CIA in premenopausal patients.

The aim of this meta-analysis was to investigate the factors responsible for the incidence of CIA and to comprehensively evaluate the prognostic role of CIA in premenopausal early-stage breast cancer patients.

Methods

The literature-search strategies, inclusion and exclusion criteria, outcome measures, and statistical analyses were performed according to the recommendations of the Cochrane Collaboration and the Quality of Reporting of Meta-analyses guidelines [13, 14].

Literature search

The systematic literature search of articles published between January 1990 and October 2013 was independently performed by two authors (J.L.Z. and J.Q.L.). A computerized search of the Medline, Embase, and Cochrane Library databases was performed without language or region restrictions. Keywords and free text searches used combinations of the following keywords: amenorrhea, breast cancer, breast neoplasm, chemotherapy, ovarian toxicity, and CIA. We also used the "related articles" function to broaden the search. The reference lists of the retrieved articles were manually searched to identify related articles. When a study generated multiple publications, either the higher quality publication or the most recent publication was included in the analysis.

Inclusion and exclusion criteria

The following inclusion criteria were applied to the included studies: (1) premenopausal patients had been pathologically diagnosed with breast cancer; (2) study reported the incidence of CIA in different chemotherapy regimens or the incidence of CIA with and without tamoxifen therapy, or the long-term OS and disease-free survival (DFS) rates were assessed as outcomes of the effect of CIA; (3) at least 20 patients were included in the study; and (4) the study was published after 1990. The following exclusion criteria were applied: (1) the inclusion criteria were not met; (2) the study supplied insufficient data, and (3) the study was not an editorial, letter, review article, case report, or animal experimental study.

Outcome measures

Outcomes assessed included the incidence of CIA in different chemotherapy regimens (anthracycline-based regimens, taxane-based regimens, cyclophosphamide-based regimen, TAC/TEC vs other three-drug combination regimens), the incidence of CIA with and without tamoxifen therapy, and long-term outcomes, including OS and DFS. Other additional outcomes that had been reported in some of the studies were also reviewed.

Data extraction and quality assessment

Two authors (J. L. Z. and J. Q. L.) independently evaluated the eligibility of potential titles and abstracts. In cases of disagreement, the authors were contacted for further information to ensure accuracy. The quality of observational studies was assessed using the modified criteria suggested by the Newcastle-Ottawa quality assessment tool [15]. The Cochrane Risk of Bias Tool was used to assess the quality of the randomized control trials (RCTs) [16]. A score of 0–9 (allocated as stars) was allocated to each observational study. RCTs and observational studies achieving six or more stars were considered to be high quality.

Data synthesis and statistical analyses

The odds ratio (OR) was used to compare dichotomous variables, and the hazard ratio (HR) was used as summary statistics for long-term survival analysis, as described by Parmar et al. [17]. All outcomes were reported with 95 % confidence intervals (CIs). Statistical heterogeneity between studies was assessed using the Chi-squared test, with significance set at $P < 0.05$. The random-effects model was used if

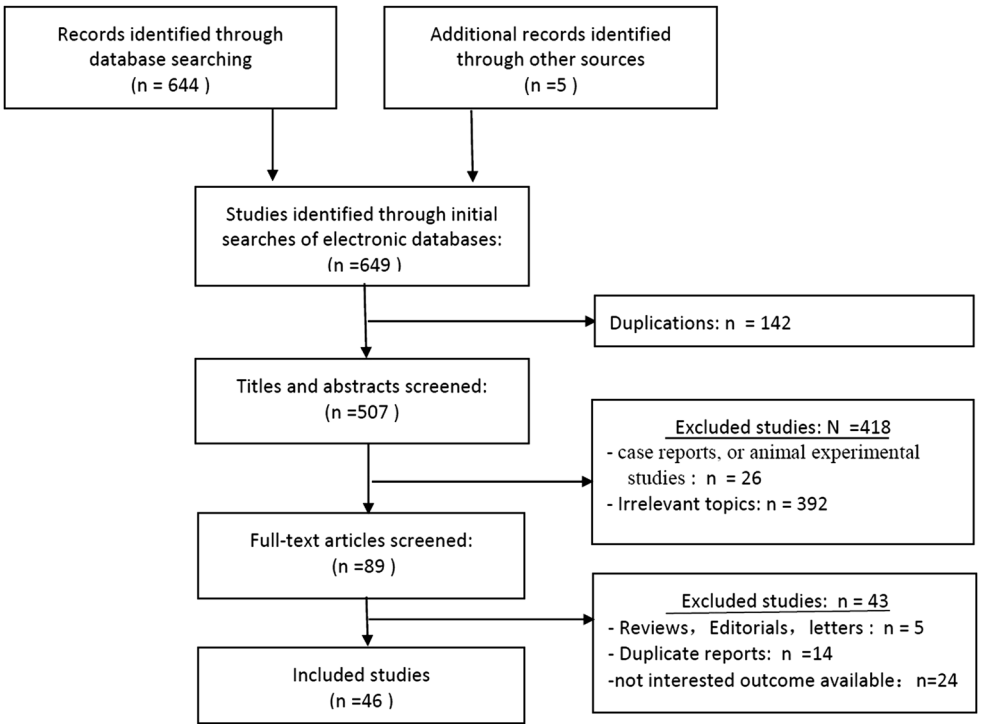

Fig. 1 Flow diagram of the studies identified, included, and excluded

there was high heterogeneity; otherwise, the fixed-effects model was reported. The quantity of heterogeneity was evaluated using the I^2 statistic. An I^2 value of <25 % was defined to represent low heterogeneity, a value between 25 and 50 % was defined as moderate heterogeneity, and >50 % was defined as high heterogeneity [18]. Subset analysis was performed to assess the efficacy of different CIA definitions and to identify the subsets of patients who were more likely to benefit from CIA. Heterogeneity between studies was evaluated using two methods: sensitivity analysis and meta-regression analysis. If there were more than three studies, including outcomes of interest, sensitivity analysis was performed for RCTs and high-quality cohort studies. If an outcome was reported in more than 10 studies, meta-regression analysis was used to find possible correlations between the publication year, study design, and outcome. Funnel plots were used to screen for potential publication bias. Statistical analyses were performed with Review Manager Version 5.1.6 and the metareg procedure in STATA 12.0. The statistical tests were two-sided, and a $P < 0.05$ was considered to be statistically significant.

Result

Flow of the included studies

Figure 1 illustrates the study screening and selection process. Forty-six studies [19] [5–12, 20–56] published from 1990 to 2013 fulfilled the inclusion criteria and were included in the current meta-analysis. In total, these studies included 15916 premenopausal breast cancer patients. The agreement between the two authors was 96 % for study selection and 94 % for quality assessment of trials.

Study characteristics

Table 1 lists the characteristics of the included studies and the details of the enrolled participants. Thirteen of the enrolled studies were RCTs, and 33 were observational studies. A total of 15,916 participants were included, and the sample size ranged from 25 to 1,885. The mean patient age ranged from 32 to 52 years, and the incidence of CIA ranged from 15 to 94 %. Breast cancer diagnoses were confirmed with postoperative pathological examination of tumor tissues. The studies were from the United Kingdom, United States, Korea, China, Spain, Iran, Finland, Switzerland, and other countries. Thirty-three studies (Table 2) assessed the incidence of CIA in different chemotherapy regimens, 15 studies (Table 3) assessed the incidence of CIA with and without tamoxifen therapy, 11 studies (Table 4) compared the DFS of breast cancer patients with CIA to that of patients without CIA, and 7 studies (Table 4) focused on OS comparison between the patients with and without CIA.

Quality of included studies

We evaluated the risk of bias in the 13 published RCTs (Supplemental Table 1) using the Cochrane risk of bias

Table 1 Characteristics of the Included Studies

Study (year)	Design	No. of pts	Age, years	Follow-up, m/y	CIA definition (lack of menstruation)	Study quality (score)
Tormey (1990) [19]	RCT	553	NA	7.7 y	≥12 m	RCT
IBCBG (1990) [20]	RCT	134	NA	96 m	≥3 m	RCT
Boccardo (1990) [21]	RCT	510	NA	40 m	≥24 m	RCT
Tormey (1992) [22]	RCT	533	44	5.1 y	≥6 m	RCT
Reyno (1993) [23]	RCT	95	NA	40 m	During follow-up	RCT
Bonadonna (1995) [24]	RCT	103	52	19.4 y	≥3 m	RCT
Pagani (1998) [25]	RCT	1196	NA	60 m	≥3 m	RCT
Goodwin (1999) [26]	R	183	43.7	NA	≥12 m	☆☆☆☆☆☆
Stone (2000) [27]	R	81	NA	NA	≥12 m	☆☆☆☆
Poikonen (2000) [28]	R	116	NA	72 m	≥6 m	☆☆☆☆☆☆☆
Borde (2003) [29]	R	1103	NA	108 m	≥6 m	☆☆☆☆☆☆
Alton (2004) [30]	P	64	NA	NA	≥12 m	☆☆☆☆
Martin (2005) [5]	RCT	823	49	55 m	≥3 m	RCT
Parulekar (2005) [31]	R	442	43.8	8.8 y	≥3 m	☆☆☆☆☆☆☆
Fornier (2005) [8]	R	166	36	37.9 m	≥12 m	☆☆☆☆☆☆☆
Davis (2005) [6]	R	159	42	NA	≥12 m	☆☆☆☆☆☆
Samuelkutty (2005) [32]	R	209	NA	18 m	NA	☆☆☆☆☆
IBCSG (2006) [11]	RCT	1246	44	7 y	≥3 m	RCT
Li (2006) [33]	R	160	42.86	72 m	≥3 m	☆☆☆☆☆☆
Kil (2006) [34]	R	160	32	54 m	NA	☆☆☆☆☆☆
Tham (2007) [9]	R	191	NA	NA	≥6 m	☆☆☆☆☆
Zhou (2007) [35]	R	103	45	NA	During follow-up	☆☆☆☆☆
Reh (2008) [36]	P	25	41	28 m	≥6 m	☆☆☆☆
Berliere (2008) [37]	R	154	NA	79 m	≥12 m	☆☆☆☆☆☆
Han (2009) [38]	P	285	40	40 m	≥3 m	☆☆☆☆☆☆☆☆
Lee (2009) [39]	R	326	42	37 m	≥6 m	☆☆☆☆☆☆
Kim (2009) [40]	R	324	40.1	31.3 m	≥3 m	☆☆☆☆☆☆
Swain (2009) [7]	RCT	708	NA	57.5 m	≥6 m	RCT
Sukumvanich (2010) [41]	P	466	39	NA	≥6 m, ≥ 12 m, ≥ 24 m	☆☆☆☆☆☆☆☆
Zhou (2010) [42]	R	170	NA	NA	NA	☆☆☆☆☆☆
Jung (2010) [43]	R	241	40	109.8 m	≥6 m	☆☆☆☆☆☆☆☆
Abusief (2010) [44]	R	431	43	33 m	≥6 m	☆☆☆☆☆☆☆
Perez-Fidalgo (2010) [45]	R	305	44	NA	≥12 m	☆☆☆☆☆☆☆☆
Rokutanda (2010) [46]	R	60	NA	NA	NA	☆☆☆☆
Swain (2010) [10]	RCT	1885	NA	73 m	≥6 m	RCT
Okanami (2011) [47]	R	77	37	27.6 m	During chemotherapy	☆☆☆☆☆
Ganz (2011) [48]	RCT	2156	NA	NA	≥6 m	RCT
Najafi (2011) [49]	R	226	40.9	43 m	≥6 m	☆☆☆☆☆☆☆☆
Arslan (2011) [50]	P	86	34	2 y	NA	☆☆☆
Zhou (2012) [51]	R	165	42	26 m	≥12 m	☆☆☆☆☆
Park (2012) [52]	R	872	41	6.2 y	≥6 m	☆☆☆☆☆☆
Narmadha (2012) [53]	R	50	40	NA	≥3 m	☆☆☆☆☆
Basso (2012) [54]	R	24	43	NA	NA	☆☆☆
Canney (2012) [55]	RCT	1333	NA	18 m	NA	RCT
Meng (2013) [56]	R	73	44	27 m	During follow-up	☆☆☆☆
Yoo (2013) [12]	P	312	43	17.5 m	≥12 m	☆☆☆☆☆☆

During chemotherapy: the patients ceased menstruation while taking chemotherapy

During follow-up: the patients ceased menstruation during the entire follow-up period

NA not available, *RCT* randomized controlled studies, *P* prospective cohort study, *R* retrospective cohort study

tool. None of the RCTs provided information regarding the blinding method. The follow-up time ranged from 18 to 233 months. For the 33 observational studies, the risk of bias was evaluated with a modification of the Newcastle-Ottawa scale (Supplemental Table 2). Twenty studies scored ≥6 stars and were considered to be of high quality. The methods for handling missing data were not adequately described in the majority of the studies.

Synthesis of results

Part one: the incidence of CIA

The incidence of CIA was significantly increased with the cyclophosphamide-based regimen (OR 2.25, 95 % CI 1.26–4.03, $P = 0.006$) compared with the regimen without cyclophosphamide (Fig. 2). The taxane-based regimen was also found to significantly increase the incidence of CIA (OR 1.24, 95 % CI 1.03–1.50, $P = 0.02$) (Fig. 3). This significant difference persisted regardless of the definition of CIA; the ORs were 1.51 (95 % CI 1.17–1.95, $P = 0.001$) (Fig. 4) when CIA was defined as >3 months without menstruation and 1.31 (95 % CI 1.06–1.62, $P = 0.01$)(Fig. 5) when CIA was defined as >6 months without menstruation. Similarly, the high CIA rate was also observed with the anthracycline/epirubicin-based regimen (OR 1.39, 95 % CI 1.15–1.70, $P = 0.0008$) (Fig. 6). We combined cyclophosphamide with anthracycline and taxanes and observed that the three-drug combination regimens were mostly likely to induce CIA (OR 1.41, 95 % CI 1.16–1.73, $P = 0.0008$)(Fig. 7).

Figure 6 shows that tamoxifen therapy significantly increased the incidence of CIA in premenopausal breast cancer patients, with an OR of 1.48 (95 % CI 1.28–1.70, $P < 0.00001$) between the two groups (Fig. 8).

Part two: long-term oncological outcomes

Table 5 presents the pooled estimate for oncological survival with and without CIA. Patients with CIA were found to have better DFS and OS, with RRs of 1.17 (95 % CI 1.05–1.31, $P < 0.00001$) and 1.15 (95 % CI 1.04–1.27, $P = 0.005$), respectively, compared with patients without CIA. The DFS advantage of CIA persisted in hormone-sensitive patients (HR 0.61, 95 % CI 0.52–0.72, $P < 0.00001$) (Fig. 9). However, in hormone-resistant patients, CIA failed to significantly affect DFS (HR 1.14, 95 % CI 0.83–1.57, $P = 0.40$) (Fig. 10).

Sensitivity analysis, meta-regression, and publication bias

Sensitivity analysis for the incidence of CIA in different chemotherapy regimens (anthracycline-based regimen, taxane-based regimen, cyclophosphamide-based regimen, and TAC/TEC vs. the other three-drug combination regimens), the incidence of CIA with and without tamoxifen therapy, and the long-term OS and DFS outcomes are shown in Table 6. The patterns of differences were similar to those of the original analysis, except that the RCTs and high-quality studies did not exhibit significant differences in the incidence of CIA with and without cyclophosphamide-based regimens. The heterogeneity among the studies was significantly reduced in the RCTs reporting the prognostic role of CIA.

Ten or more studies assessed the incidence of CIA with and without the taxane-based regimen, the incidence of CIA with and without the anthracycline-based regimen, the incidence of CIA with and without tamoxifen therapy, and the DFS of breast cancer patients with and without CIA. Meta-regression analysis revealed no significant correlations between the publication year, the study design, and the four outcomes described above.

Rank correlation analysis of the funnel plot did not reveal any significant graphic or statistical bias (Supplemental Figs. 1–7).

Discussion

Adjuvant chemotherapy can prolong OS in women with early-stage breast cancer, even in patients with endocrine-responsive disease. As a consequence of chemotherapy, women who are premenopausal at the time of onset will develop transient amenorrhea (CIA). Although the majority of studies have found that this ovarian toxicity caused by chemotherapy may predict better clinical outcomes [57, 58], CIA causes significant adverse effects, including sexual dysfunction, psychological problems, and bone loss, as well as a lower rate of subsequent pregnancy, with an overall negative impact on quality of life [59]. Therefore, CIA is an important issue that is of particular interest to breast oncologists.

The risk of CIA depends on the patient age, type and doses of chemotherapy, and use of tamoxifen [58]. The impact of age on CIA is similar in most studies. Older women (over 40 years old) have a higher incidence of CIA (range 40–100 %) compared with younger women (range 21–71 %) [26, 60–63]. However, the influence of different types of chemotherapy on the risk of CIA remains controversial. For the anthracycline-based regimens, some studies reported that patients treated with AC or CEF exhibited significantly lower rates of amenorrhea after one year than those patients treated with classic CMF [26, 64]; however, the NCIC CTG MA.5 trial reported higher rates of amenorrhea with an anthracycline-based chemotherapy compared with CMF [31]. When taxanes are added to

Table 2 Incidence of amenorrhea with different chemotherapy regimens

Author (year)	Design	No. of pts	CIA definition	Treatment regimen	CIA (%)
Tormey (1992) [22]	RCT	533	≥6 m	CMFPT	25
				ALTER	24
Goodwin (1999) [26]	R	183	≥12 m	CMF	65
				CEF	56
Stone (2000) [27]	R	81	≥12 m	AC	43
				AC + T	38
Alton (2004) [30]	P	64	≥12 m	AC + T	53
				AC	69
Martin (2005) [5]	RCT	823	≥3 m	TAC	62
				FAC	52
Parulekar (2005) [31]	R	442	≥3 m	CEF	ER + 76,ER-67
				CMF	ER + 65,ER-58
Davis (2005) [6]	R	159	≥12 m	ACT CAFT CMFT	43
				AC CAF CMF	52
Samuelkutty (2005) [32]	R	209	NA	EC-T	64
				CEF/CMF	61
Li (2006) [33]	R	160	≥3 m	FEC	70
				Taxane-based chemotherapy	69
				CMF	45
Kil (2006) [34]	R	160	NA	CMF	31
				AC	38
				CAF	52
Tham (2007) [9]	R	191	≥6 m	AC	55
				AC-T	64
Zhou (2007) [35]	R	103	During follow-up	Anthracycline-based chemotherapy	91
				Docetaxel-based chemotherapy	89
Reh (2008) [36]	P	25	≥6 m	ACT	36
				AC	9
Berliere (2008) [37]	R	154	≥12 m	6FEC	93
				3FEC-3T	93
Han (2009) [38]	P	285	≥3 m	TX/AC	98
				AC-T	88
				FAC	81
Lee (2009) [39]	R	326	≥6 m	FAC or AC	57
				FACT or ACT	58
				CMF	56
Kim (2009) [40]	R	324	≥3 m	CMF	81
				Anthracycline/taxane-based chemotherapy	78
Sukumvanich (2010) [41]	P	466	≥6 m, ≥12 m, ≥24 m	AC	(CIA ≥ 6 m) 37 (CIA ≥ 12 m) 19
				ACT	(CIA ≥ 6 m) 4 5 (CIA ≥ 12 m) 29
				CMF	(CIA ≥ 6 m) 34 (CIA ≥ 12 m) 30

Table 2 continued

Author (year)	Design	No. of pts	CIA definition	Treatment regimen	CIA (%)
Zhou (2010) [42]	R	170	NA	FEC	45
				TE	30
				NE	23
Jung (2010) [43]	R	241	≥6 m	FAC	68
				CMF	52
Abusief (2010) [44]	R	431	≥6 m	AC	55
				AC and paclitaxel*4	58
				AC and paclitaxel*12	48
Perez-Fidalgo (2010) [45]	R	305	≥12 m	Anthracycline-based chemotherapy	75
				Anthracycline and taxane-based chemotherapy	83
Rokutanda (2010) [46]	R	60	NA	Anthracycline-based chemotherapy	73
				Anthracycline and taxane-based chemotherapy	87
Okanami (2011) [47]	R	77	During chemotherapy	A	71
				A + T	94
Ganz (2011) [48]	RCT	2156	≥6 m	AC-T	83
				AT	47
				TAC	67
Najafi (2011) [49]	R	226	≥6 m	CMF	53
				AC/CAF	67
				AC-T	79
Arslan (2011) [50]	P	86	NA	ACT	67
				AC	42
Zhou (2012) [51]	R	165	≥12 m	FEC	49
				sequential-ECT	42
				FEC-T	21
				concurrent-ECT	44
Narmadha (2012) [53]	R	50	≥3 m	FAC/FEC	75
				TAC/TEC	100
Basso (2012) [54]	R	24	NA	AC	90
				ACT	83
				AC-T	100
Canney (2012) [55]	RCT	1333	NA	E-CMF	69
				aE-CMF	67
				E-X	28
				aE-X	29
Meng (2013) [56]	R	73	During follow-up	FEC	80
				TC/TCH	95
				TEC/FEC-T/TE	79
Yoo (2013) [12]	P	312	≥12 m	AC	91
				AC-T	98

During chemotherapy: the patients ceased menstruation while taking chemotherapy. During follow-up: the patients ceased menstruation during the entire follow-up period

RCT randomized controlled studies, *P* prospective cohort study, *R* retrospective cohort study, *NA* not available, *CMF* cyclophosphamide/methotrexate/fluorouracil, *CEF* cyclophosphamide/epirubicin/fluorouracil, *AC* doxorubicin/cyclophosphamide, *EC* epirubicin/cyclophosphamide, *FEC* fluorouracil/epirubicin/cyclophosphamide, *AC-T* doxorubicin/cyclophosphamide-taxane, *AT* doxorubicin/taxane

Table 3 Incidence of amenorrhea with or without Tamoxifen

Author (year)	Design	No. of pts	Follow-up	CIA definition (m)	Treatment regimen	CIA (%)	
						with TAM	without TAM
Boccardo (1990) [21]	RCT	510	40 m	≥24	CMF-E	75	74
Pagani (1998) [25]	RCT	1196	60 m	≥3	CMF	63	57
Goodwin (1999) [26]	R	183	NA	≥12	CMF/CEF	84	63
Fornier (2005) [8]	R	166	37.9 m	≥12	AC-paclitaxel	17	13
Davis (2005) [6]	R	159	NA	≥12	ACT CAFT CMFT/AC CAF CMF	51	47
IBCSG (2006) [11]	RCT	1246	7 y	≥3	AC/EC-CMF	89	84
Tham (2007) [9]	R	191	NA	≥6	AC/AC-T	63	58
Han (2009) [38]	P	285	40 m	≥3	TX/AC/AC-TFAC	90	87
Swain (2009) [7]	RCT	708	57.5 m	≥6	AC-T	31	19
Zhou (2010) [42]	R	170	NA	NA	FEC/TE/NE	44	17
Jung (2010) [43]	R	241	109.8 m	≥6	FAC/CMF	64	47
Najafi (2011) [49]	R	226	43 m	≥6	CMF/AC/CAF/AC-T	68	68
Zhou (2012) [51]	R	165	26 m	≥12	FEC/sequential-ECT/FEC-T/ECT	44	42
Meng (2013) [56]	R	73	27 m	During follow-up	FEC/TC/TCH/TEC/FEC-T/TE	86	67
Yoo (2013) [12]	P	312	17.5 m	≥12	AC/AC-T	97	87

During chemotherapy: the patients ceased menstruation while taking chemotherapy

During follow-up:the patients ceased menstruation during the entire follow-up period

RCT randomized controlled studies, *P* prospective cohort study, *R* retrospective cohort study, *NA* not available, *CMF* cyclophosphamide/methotrexate/fluorouracil, *CEF* cyclophosphamide/epirubicin/fluorouracil, *AC* doxorubicin/cyclophosphamide, *EC* epirubicin/cyclophosphamide, *FEC* fluorouracil/epirubicin/cyclophosphamide, *AC-T* doxorubicin/cyclophosphamide-taxane, *AT* doxorubicin/taxane

standard regimens, the risk of CIA increased in the majority of studies [5, 8, 9, 38, 42, 49] but decreased in other trials [37, 39, 45, 47]. The current meta-analysis (Part One in Results) revealed that when taxanes were added to or were part of standard regimens, CIA rates increased significantly, regardless how CIA was defined (e.g., lack of menstruation for >3 months or >6 months). Similar results were observed when the anthracycline/epirubicin combination was added to standard regimens. In addition, our analysis also revealed that cyclophosphamide-based regimens were associated with a higher risk of CIA, which is consistent with most of the studies [9, 60]. Because anthracycline/epirubicin, taxanes and cyclophosphamide all contribute to higher rates of CIA, we infer that the TAC/TEC regimen is associated with the highest rate of CIA compared with other three-drug combination regimens. The result of our meta-analysis confirmed our hypothesis. Note that tamoxifen is the classic endocrine drug for premenopausal endocrine-responsive breast cancer patients, and tamoxifen is associated with an elevated rate of CIA in most large prospective trials [7, 11, 21, 25, 26, 65]. We enrolled both prospective and retrospective studies and conducted a meta-analysis, the result (Part One in Results) of which emphasized the impact of tamoxifen on the risk of CIA.

Although CIA was found to positively impact patient outcomes (DFS and/or OS) in the majority of prospective/retrospective studies (Table 4) and although our meta-analysis confirmed the significant influence of CIA on patient prognosis (DFS and OS) (Part Two in Results), several questions related to this issue remain unanswered. As the significance of molecular subtypes is widely accepted by breast surgeons and oncologists in the prognosis and treatment of early-stage breast cancer, clinicians want to determine whether CIA could predict better clinical outcomes for all types of early breast cancer patients or only for distinct subtypes of patients. The largest prospective trial, NSABP B-30, revealed that CIA was associated with improved survival regardless of ER status [10], and this finding is consistent with a previous trial (ECOGT) [22]. However, other RCTs, such as the IBCSG Trial 13–93, IBCSG Trial VI and Trial VIII, and the 12-month landmark analysis of the NSABP B-30 trial, reported contradictory results that the positive influence of CIA was restricted to ER-positive breast cancer patients [10, 11, 25, 66]. To address this issue, we enrolled four studies that analyzed the outcomes of both ER-positive and ER-negative patients, and we performed a meta-analysis. The reason we have not enrolled the NSABP B-30 trial is that we could not obtain the detailed DFS data for analysis. Because only two of the four studies reported detailed OS data, we could not perform the meta-analysis on OS for either ER-positive or ER-negative patients. However, our meta-analysis (Part Two in Results) suggested that CIA

Table 4 Correlation between CIA and survival

Author (year)	Design	No. of pts	Follow-up	CIA definition (m)	Outcome benefit	*P*
IBCBG (1990) [20]	RCT	134	96 m	≥3	DFS benefit	NS
Tormey (1992) [22]	RCT	533	5.1 y	≥6	DFS benefit	0.04 (DFS)
					OS benefit	0.04 (OS)
Reyno (1993) [23]	RCT	95	40 m	During follow-up	RFS benefit	0.03 (RFS)
					OS benefit	0.17 (OS)
Bonadonna (1995) [24]	RCT	103	19.4 y	≥3	RFS benefit	NS
Pagani (1998) [25]	RCT	1196	60 m	≥3	DFS benefit in ER+	0.0001
Poikonen (2000) [28]	R	116	72 m	≥6	DFS benefit	0.02 (DFS)
					OS benefit	0.05 (OS)
Borde (2003) [29]	R	1103	108 m	≥6	DFS benefit	0.001 (DFS)
					OS benefit	0.001 (OS)
Parulekar (2005) [31]	R	442	8.8 y	≥3	DFS benefit in ER+	0.005
					OS benefit ER+	0.002
IBCSG (2006) [11]	RCT	1246	7 y	≥3	DFS benefit in ER+	0.004
Li (2006) [33]	R	160	72 m	≥3	DFS benefit	0.04
Kil (2006) [34]	R	160	54 m	NA	RFS Benefit	0.89
Jung (2010) [43]	R	241	109.8 m	≥6	DFS benefit in HR+	0.025 (DFS)
					OS benefit in HR+	0.048 (OS)
Swain (2010) [10]	RCT	1885	73 m	≥6	DFS benefit in HR+	<0.001 (DFS)
					OS benefit in HR+	0.002 (OS)
Park (2012) [52]	R	872	6.2 y	≥6	DFS benefit	0.452

During chemotherapy: the patients ceased menstruation while taking chemotherapy

During follow-up: the patients ceased menstruation during the entire follow-up period

RCT randomized controlled studies, *P* prospective cohort study, *R* retrospective cohort study, *NA* not available, *CMF* cyclophosphamide/methotrexate/fluorouracil, *CEF* cyclophosphamide/epirubicin/fluorouracil, *AC* doxorubicin/cyclophosphamide, *EC* epirubicin/cyclophosphamide, *FEC* fluorouracil/epirubicin/cyclophosphamide, *AC-T* doxorubicin/cyclophosphamide-taxane, *AT* doxorubicin/taxane

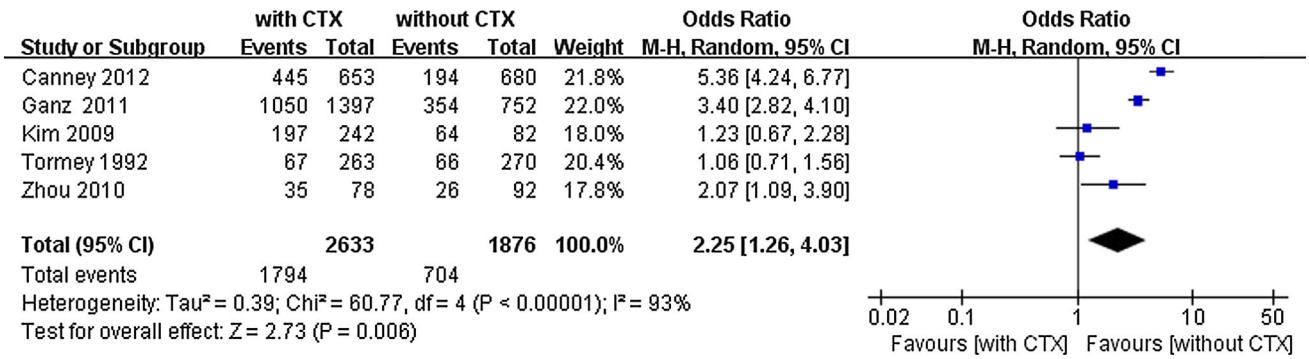

Fig. 2 Incidence of CIA with and without the cyclophosphamide-based regimen

predicted longer DFS only in ER-positive early-stage breast cancer patients. Although the meta-analysis did not review data from the NSABP B-30 trial, our finding is consistent with the 12-month conditional landmark analysis of this trial [10], which we think it might be more accurate because the landmark analysis might minimize the guarantee-time bias, and the final result of IBCSG Trial 13–93 is the 18-month landmark analysis of the original data [67]. Nevertheless, the positive influence of CIA on prognosis should be interpreted with caution. Note that age is an independent factor that affects prognosis, and large studies in Europe (IBCSG), Korea, and China have demonstrated that older patients (over 40 years old) exhibited better prognoses than younger women, particularly for patients with ER-positive breast cancer subtypes [68–70]. As mentioned above, older women (over 40 years old) had

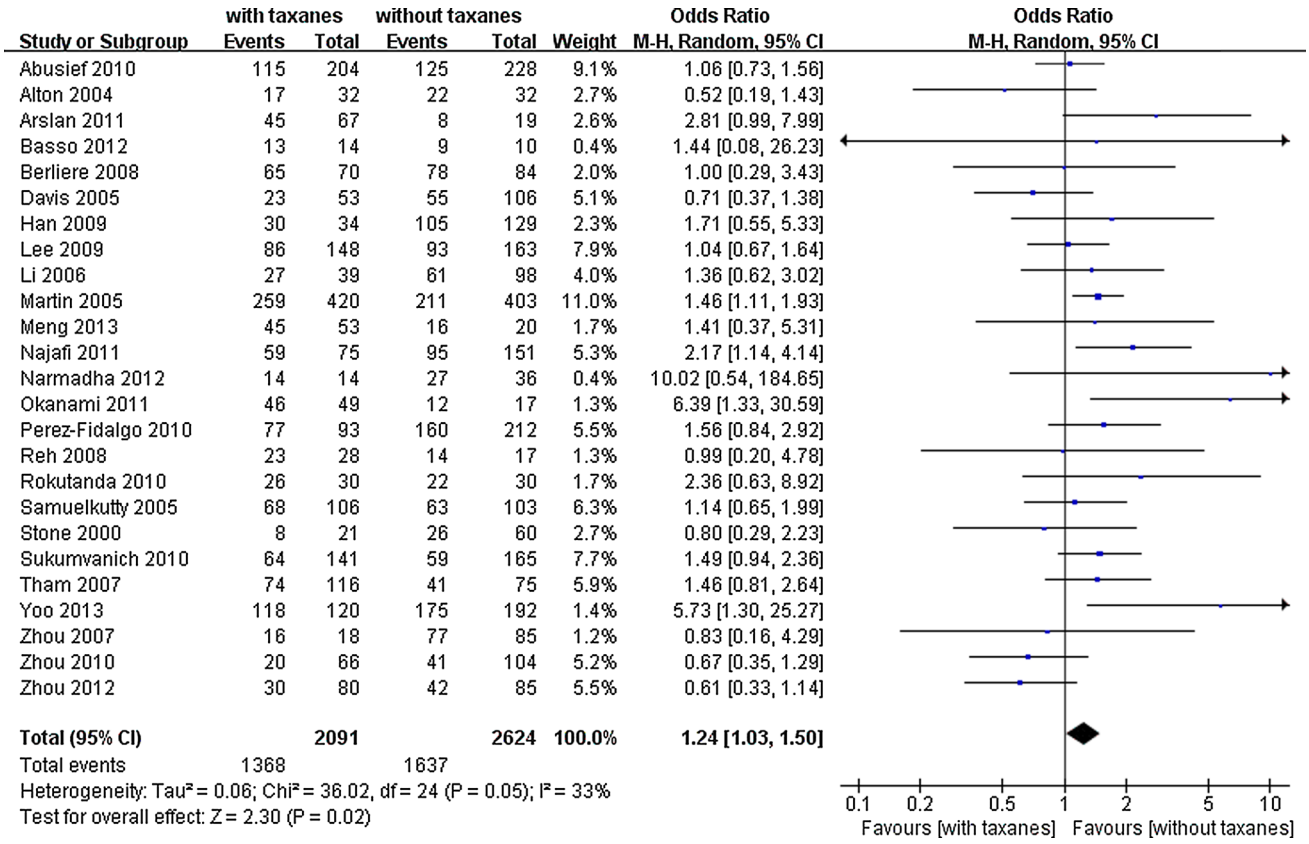

Fig. 3 Incidence of CIA with and without the taxane-based regimen

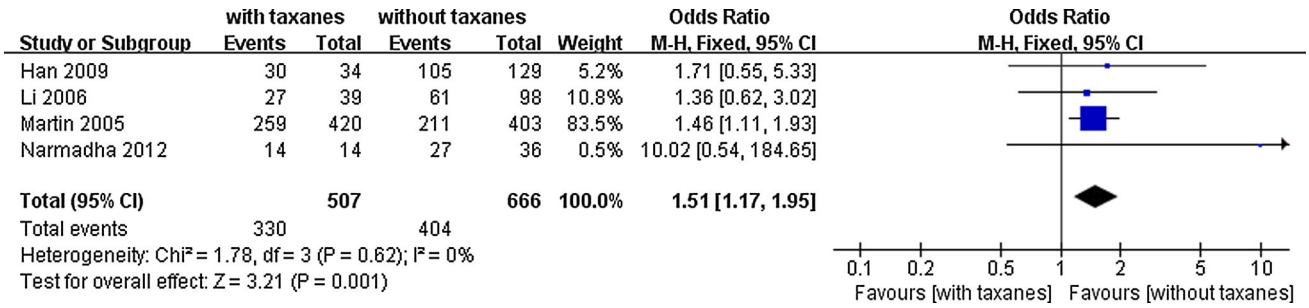

Fig. 4 Incidence of CIA with and without the taxane-based regimen (CIA, no menstruation for more than three months)

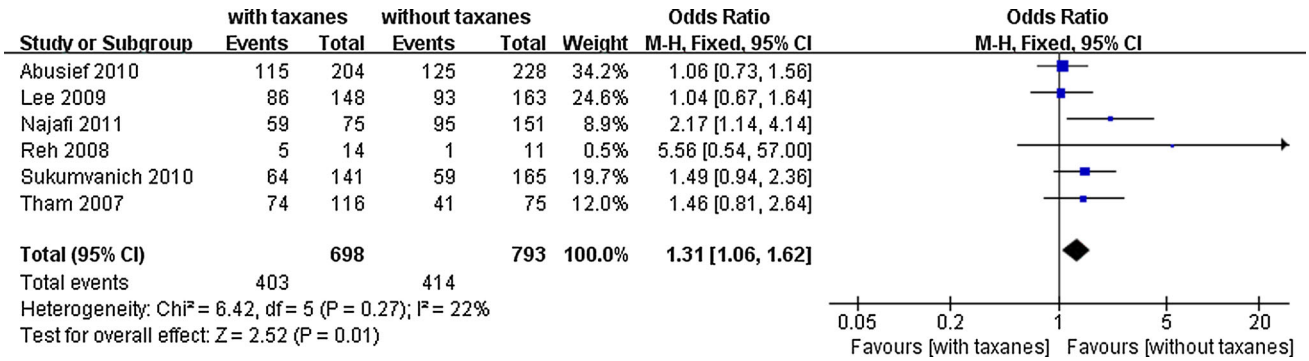

Fig. 5 Incidence of CIA with and without taxane-based regimen (CIA, no menstruation for more than six months)

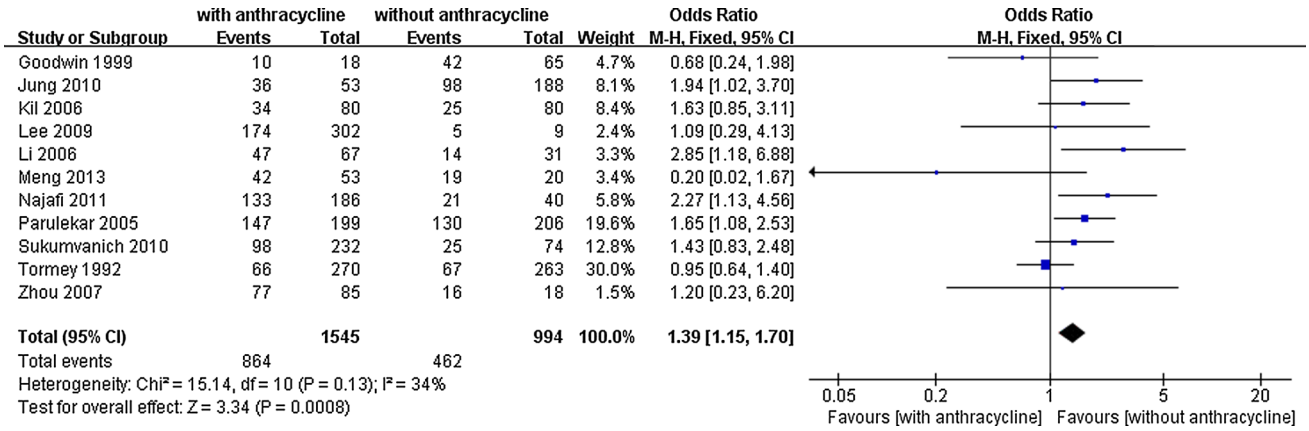

Fig. 6 Incidence of CIA with and without the anthracycline/epirubicin-based regimen

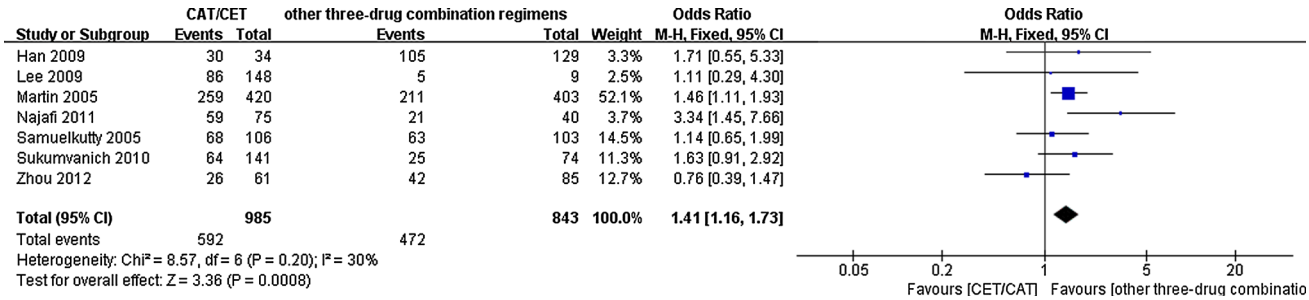

Fig. 7 Incidence of CIA (CAT/CET vs other three-drug combination regimens)

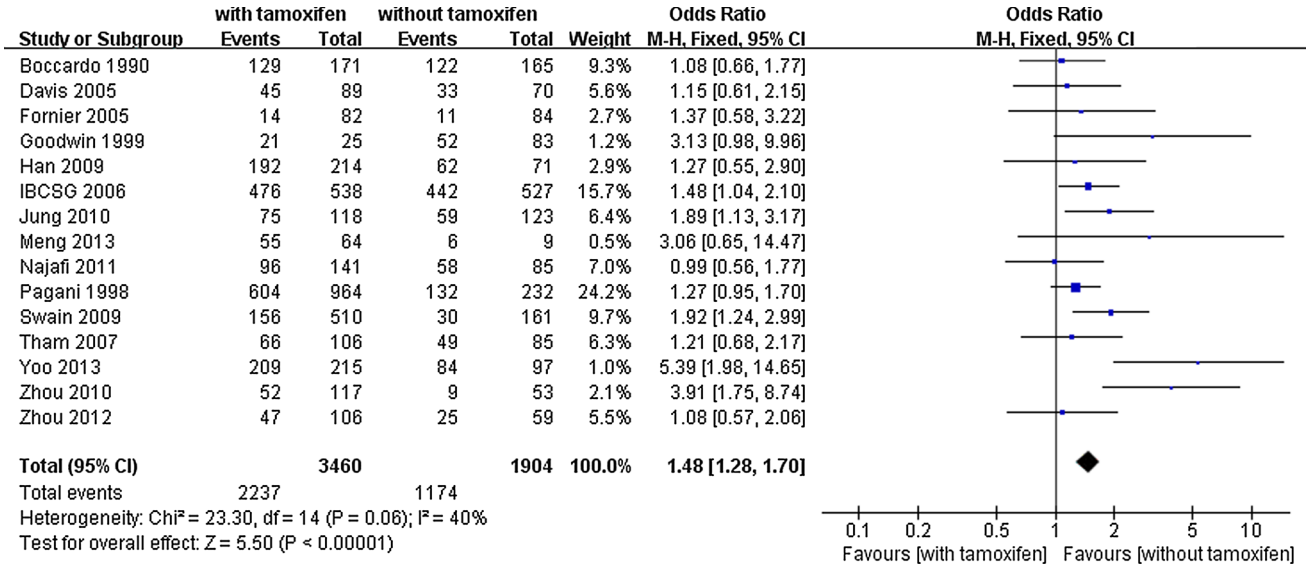

Fig. 8 Incidence of CIA with and without tamoxifen

a higher incidence of CIA compared with younger women; we cannot obviate the possibility that age contributes to the positive effect of CIA on prognosis. Moreover, the subset analysis of the Bonadonna, G., et al. study and the IBCSG trail VI both found that CIA was not associated with better prognosis after adjusting for age [24, 25]; the results of these two studies conflict with the subset analysis of the NSABP B-30 trial, which demonstrated that the effect of CIA remained significant after adjusting for age [10]. Therefore, further well-designed RCTs analyzing the

Table 5 Overall analysis of the patients with CIA versus the patients without CIA

Outcome of interest	No. of studies	OR/RR/HR (95 % CI)	*P*	Study heterogeneity			
				Chi squared test	df	I^2 (%)	*P*
Part one: incidence of CIA							
Incidence of CIA with and without cyclophosphamide-based regimen	5	2.25 (1.26, 4.03)	0.006	60.77	4	93	<0.00001
Incidence of CIA with and without taxane-based regimen	25	1.24 (1.03, 1.50)	0.02	36.02	24	33	0.05
Incidence of CIA with and without anthracycline-based regimen	11	1.39 (1.15, 1.70)	0.0008	15.14	10	34	0.13
Incidence of CIA (CAT/CET vs other three-drug combination regimens)	7	1.41 (1.16, 1.73)	0.0008	8.57	6	30	0.2
Incidence of CIA with and without tamoxifen	15	1.48 (1.28, 1.70)	<0.0001	23.3	14	40	0.06
Part two: long-term oncological outcomes							
DFS with and without CIA (all)	10	1.17 (1.05, 1.31)	0.005	77.02	9	88	<0.00001
DFS with and without CIA (HR +)	4	0.61 (0.52, 0.72)	<0.00001	1.48	3	0	0.686
DFS with and without CIA (HR–)	4	1.14 (0.83, 1.57)	0.40	1.12	3	0	0.773
OS with and without CIA	6	1.15 (1.04, 1.27)	0.005	24.52	5	80	0.0002

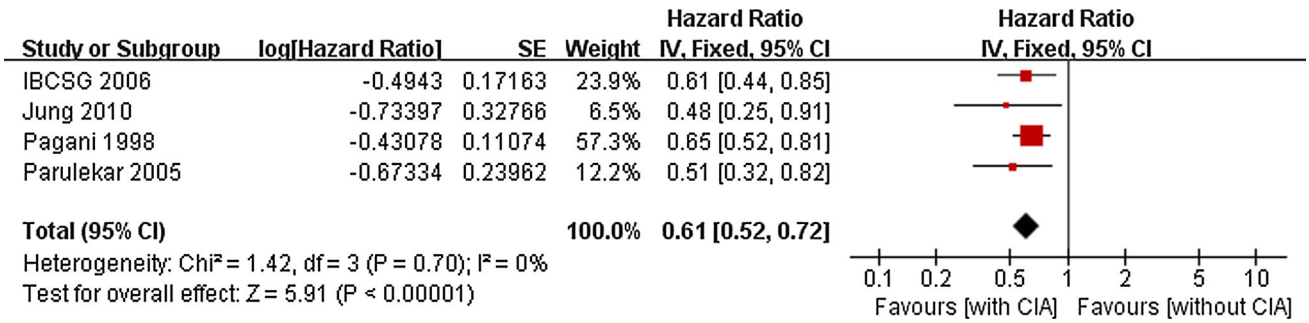

Fig. 9 DFS with and without CIA (ER +)

influence of CIA on prognosis after adjusting for age and ER status or multivariate analyses of age in different of breast cancer patients subgroups are needed to further elucidate this issue.

The causality between CIA and clinical outcomes remains unclear. We are uncertain whether CIA is a cause or merely an indicator of better prognosis. If CIA is the direct cause of better prognosis, we are concerned with the oncological safety of the fertility preservation approach in premenopausal breast cancer women, particularly in ER-positive breast cancer patients. CIA is the only surrogate marker of infertility in the current studies, and GnRHa was used to reduce the incidence of CIA when fertility preservation was performed. We suggest that without solid evidence, fertility preservation study should only be conducted in ER-negative breast cancer patients.

Regarding concerns of the impact of CIA on quality of life, few studies have reported detailed data. Sandra M. Swain, et al. [7] used the FACT-B and menopausal symptoms questionnaires to study the quality of life of patients with CIA in the NSABP B-30 trial, and the authors found that CIA had no significant negative impact on physical well-being, social well-being, emotional well-being, or menopausal symptoms [48]. This result is

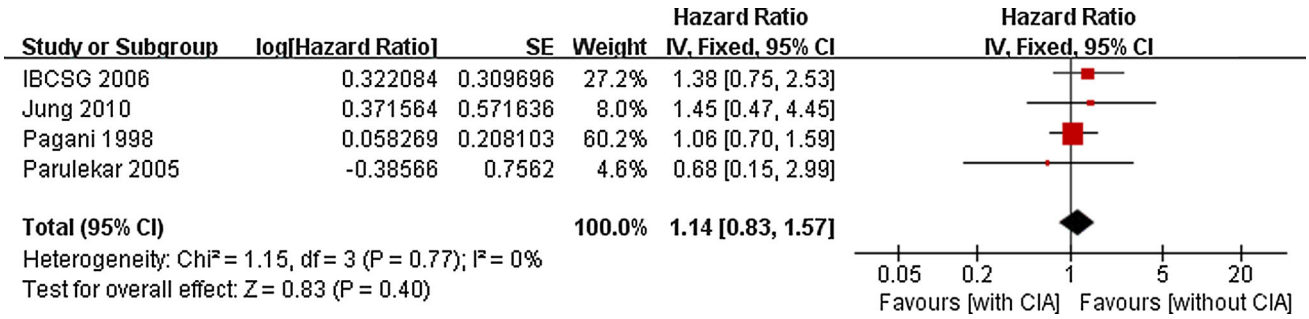

Fig. 10 DFS with and without CIA (HR–)

Table 6 Sensitivity analysis of patients with and without CIA

Outcome of interest	No. of studies	OR/RR/HR (95 % CI)	P	Study heterogeneity			
				Chi squared test	df	I^2 (%)	P
Analysis of RCTs							
Incidence of CIA with and without cyclophosphamide-based regimen	3	2.73 (1.32, 5.66)	0.007	48.57	2	96	<0.00001
Incidence of CIA with and without taxane-based regimen	2	1.38 (1.10, 1.75)	0.006	0.54	1	0	0.46
Incidence of CIA with and without anthracycline-based regimen	1	NA	NA	NA	NA	NA	NA
Incidence of CIA (CAT/CET vs other three-drug combination regimens)	1	NA	NA	NA	NA	NA	NA
Incidence of CIA with and without tamoxifen	4	1.40 (1.17, 1.69)	0.0003	3.58	3	16	0.31
DFS with and without CIA (all)	5	1.16 (1.10, 1.22)	<0.00001	0.93	4	0	0.92
DFS with and without CIA (HR +)	2	0.64 (0.53, 0.76)	<0.0001	0.1	1	0	0.75
DFS with and without CIA (HR–)	2	1.15 (0.82, 1.63)	0.423	0.48	1	0	0.487
OS with and without CIA	3	1.09 (1.04, 1.14)	0.00004	0.09	2	0	0.96
High-quality observational studies (≥6 stars) and RCTs							
Incidence of CIA with and without cyclophosphamide-based regimen	5	1.97 (0.76, 5.12)	0.16	60.11	3	95	<0.00001
Incidence of CIA with and without taxane-based regimen	13	1.29 (1.12, 1.48)	0.0005	17.25	12	30	0.14
Incidence of CIA with and without anthracycline-based regimen	9	1.44 (1.18, 1.76)	0.0003	11.79	8	32	0.16
Incidence of CIA (CAT/CET vs other three-drug combination regimens)	5	1.58 (1.26, 1.99)	<0.0001	3.69	4	0	0.45
Incidence of CIA with and without tamoxifen	12	1.58 (1.26, 1.98)	<0.0001	21.14	11	48	0.03
DFS with and without CIA (all)	10	1.18 (1.03, 1.35)	0.02	78.75	8	90	<0.00001
DFS with and without CIA (HR +)	4	0.56 (0.44, 0.72)	<0.0001	0.63	2	0	0.73
DFS with and without CIA (HR–)	4	1.29 (0.77, 2.14)	0.334	0.79	2	0	0.674
OS with and without CIA	6	1.17 (1.03, 1.33)	0.02	20.53	4	81	0.0004

consistent with the study by Carey Anders et al. [71], but a recent study in Korea suggested that CIA was associated with patients' vasomotor, psychosocial, physical, and sexual dysfunctions [12]. Therefore, we think that CIA might have some negative impacts on quality of life, particularly on patients' psychological health and sexual lives, and physicians should pay more attention to these concerns.

In our attempt to review the literature, we were surprised to discover that few studies have evaluated the impact of CIA on the outcomes of both ER-positive and ER-negative patients. In the four enrolled studies, the definition of CIA differed based on how long menstruation had ceased, varying from 3 to 6 months. Therefore, the small number of enrolled randomized studies and the distinct definitions

of CIA might make it difficult to acquire enough data for valuable results.

Conclusions

In summary, the current meta-analysis demonstrated that when anthracycline/epirubicin, taxanes or cyclophosphamide was added to standard regimens, CIA rates increased significantly. The TAC/TEC regimen was associated with the highest rate of CIA compared with the other three-drug combination regimens. More interesting, our analysis indicated that CIA predicted better outcomes (DFS/OS) in premenopausal women (when analyzed for the whole population), and CIA was associated with longer DFS, particularly in ER-positive premenopausal early-stage breast cancer patients. These results suggest that CIA is not merely a side effect of chemotherapy, it is a better prognosis marker, particularly for ER-positive, premenopausal, early-stage breast cancer patients who have undergone chemotherapy. However, this finding merits future randomized control studies to analyze the associations between CIA and patient prognosis after adjusting for age, ER status, and other influential factors.

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Conflict of interest The authors have reported no conflicts of interest.

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