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Prognostic impact of chemotherapy-induced amenorrhea on premenopausal breast cancer: a meta-analysis of the literature

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Abstract

Objective: We conducted this meta-analysis of published data to assess the exact prognostic value of adjuvant chemotherapy-induced amenorrhea (CIA) as a prognostic factor for premenopausal breast cancer.

Methods: We searched for all relevant studies published before May 2014 in the PubMed, OVID, and EMBASE databases. Relative risks (RRs) were used to estimate the association between CIA and various survival outcomes, including disease-free survival (DFS) and overall survival (OS).

Results: This meta-analysis identified 13 eligible studies including 5,513 cases and 2,008 controls for DFS and 5 eligible studies including 2,331 cases and 776 controls for OS. Results demonstrated that CIA is associated with improved DFS (RR, 0.67; 95% CI, 0.61-0.74; $P < 0.001$) and OS (RR, 0.60; 95% CI, 0.50-0.72; $P < 0.001$). In subgroup analyses, CIA was found to affect DFS (RR, 0.73; 95% CI, 0.61-0.88; $P = 0.001$) in estrogen receptor (ER)–positive patients; however, similar results were not observed in ER-negative patients (for DFS: RR, 0.97; 95% CI, 0.66-1.41; $P = 0.858$). Participants with CIA achieved a significantly better prognosis than participants without CIA, irrespective of nodal status, chemotherapy regimen, endocrine therapy, or publication year.

Conclusions: This meta-analysis clarifies that CIA contributes to improved prognosis in premenopausal women with ER-positive breast cancer and is at least partially responsible for the benefits of adjuvant chemotherapy in these women, which induce chemical castration.

Key Words: Breast neoplasm – Chemotherapy-induced amenorrhea – Meta-analysis – Prognosis.

Adjuvant chemotherapy and endocrine therapy have been confirmed to increase survival and to reduce the risk of recurrence of breast cancer.[1-3] Interestingly, in 1987, Brincker et al[4] hypothesized that adjuvant cytotoxic chemotherapy might exert cytotoxic effects and induce chemical castration because such chemotherapy is consistently more effective in premenopausal women than in postmenopausal women. It is not clear whether chemotherapy-induced amenorrhea (CIA) impacts prognosis or is merely a marker of the negative effects of chemotherapy on ovarian function; in the 1990s, there was a debate regarding the prognostic role of CIA.[5,6]

A growing number of studies have assessed the role of CIA in premenopausal breast cancer; however, the results have been inconsistent. For example, in the review conducted by Walshe et al,[7] 15 of 23 studies suggested that CIA has a favorable effect on the prognosis of breast cancer, whereas another 8 studies did not support this result. In addition, Swain et al[8] reported that amenorrhea is related to improved survival based on estrogen receptor (ER) status; however, another study showed that CIA might have a beneficial effect on disease-free survival (DFS) and overall survival (OS) in women with hormone receptor–positive breast cancer.[9]

We conducted a meta-analysis of published data to assess the exact prognostic value of CIA in premenopausal women with breast cancer who are undergoing adjuvant chemotherapy.

METHODS

Search strategy

"Amenorrhea" and "breast cancer" were searched as subject headings and key words in the PubMed, OVID, and EMBASE databases for the period between January 1966 and May 2014. The computer search identified 649 articles after removal of duplicates. Review articles and

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conference abstracts were also obtained to identify potentially eligible studies. The search results were scanned according to the following inclusion criteria: association between CIA and prognostic factors for breast cancer; sufficient data to allow estimates of relative risks (RRs; with 95% CIs) for DFS (defined as the time from the date of diagnosis to the date before local, regional, or distant recurrent breast cancer; occurrence of contralateral breast cancer; occurrence of a second primary cancer; or death from any cause) and OS (defined as the time from the date of diagnosis to the date of death from any cause); and publication in English. Letters to the editors, reviews, research protocols, articles based on guidelines, articles published in a book, and articles published in non–English-language journals were excluded. Statistical data were retrieved from 13 articles, including prospective and retrospective studies (Table 1). When various publications related to the same study were identified, we used the most recent publication containing data that were sufficient for calculations. Q.Z., W.Y., and Y.D., conducted the literature search. Articles were selected after discussion among J.L., Q.Z., W.Y., and Y.D. The following information was extracted from each publication: publication year, first author's surname, number of cases and controls, number of different clinical and pathologic parameters, and survival assessment methods. The citation lists associated with all of the studies retrieved in the search were used to identify other potentially relevant publications.

Statistical analysis

RR was used as a measure of risk to estimate the association between CIA and breast cancer outcome. When RRs were not given directly, the original data and figures from the published articles were used to estimate the RRs according to the methods described by Parmar et al[20] In each study, between-study heterogeneity was assessed by χ^2-based Q statistics and by I^2 test. When $P < 0.1$ or I^2 was higher than 50%, heterogeneity was considered to exist, and RRs were calculated using a random-effects model (DerSimonian-Laird method); otherwise, a fixed-effects model (Mantel-Haenszel method) was applied. These two methods provide similar results when there is no between-study heterogeneity. Funnel plots and Egger's test were performed to determine potential publication bias. Sensitivity analyses were used to estimate the influence of individual studies on summary effect.

Based on lymph node status, the studies were divided into lymph node–positive or unclassified. Based on ER status, the studies were classified as ER-positive, ER-negative, or unclassified. For the subgroup analysis of chemotherapy regimens, the studies were classified as anthracycline, taxane, or nonanthracycline/nontaxane. For endocrine therapy, the studies were divided into three subgroups: with endocrine therapy, without endocrine therapy, and unclassified. For publication year, the studies were classified as published after 2000 or published before 2000. Kaplan-Meier curves were analyzed using free software (GetData Graph Digitizer 2.24; http://getdata-graph-digitizer.com). All statistical analyses were performed using Stata/SE version 11.0 for Windows (StataCorp, College Station, TX).

RESULTS

Characteristics of the studies

Thirteen studies were included in our analysis.[4,8-19] Two participant cohorts were included in the studies conducted by Parulekar et al[14] and Brincker et al,[4] and the Kaplan-Meier method was used for measurements in three articles.[4,13,18] A total of 5,513 women with CIA were compared with a control group comprising 2,008 women to analyze DFS, whereas

TABLE 1. *Studies included in the meta-analysis: endocrine therapy, type of study, and definition of CIA*

Study	Endocrine therapy	Prospective or retrospective study	Single-institution or multicenter study	Definition of CIA
Jung et al[9]	5 y for HR^+	Retrospective	Single institution	≥6 mo
Swain et al[8]	5 y for HR^+	Prospective	Multicenter	≥6 mo
Kil et al[10]	Not mentioned	Retrospective	Single institution	Not mentioned
Gnant et al[11]	No participants received endocrine therapy	Prospective	Multicenter	Not mentioned
Colleoni et al[12]	5 y for ER^+	Prospective	Multicenter	Arising within 15 mo of randomization
Vanhuyse et al[13]	No participants received endocrine therapy	Retrospective	Not mentioned	Arising within 12 mo of chemotherapy
Parulekar et al[14] (HR^+)	No participants received endocrine therapy	Retrospective	Not mentioned	≥3 mo
Parulekar et al[14] (HR^-)	No participants received endocrine therapy	Retrospective	Not mentioned	≥3 mo
Jonat et al[15]	No participants received endocrine therapy	Prospective	Multicenter	Arising within 3 mo of chemotherapy
Pagani et al[16]	Not mentioned	Prospective	Multicenter	≥3 mo
Bianco et al[17]	Not mentioned	Prospective	Not mentioned	≥3 mo
Goldhirsch et al[18]	Not mentioned	Prospective	Multicenter	≥3 mo
Brincker et al[4] (chemotherapy)	Not mentioned	Prospective	Multicenter	Arising within 12 mo
Brincker et al[4] (CMF)	Not mentioned	Prospective	Multicenter	Arising within 12 mo
Ludwig Breast Cancer Study Group[19]	Not mentioned	Prospective	Multicenter	Not mentioned

CIA, chemotherapy-induced amenorrhea; HR^+, hormone receptor–positive; ER^+, estrogen receptor–positive; HR^-, hormone receptor–negative; CMF, cyclophosphamide/methotrexate/fluorouracil.

TABLE 2. *Studies included in the meta-analysis: sample size, treatment regimen, median follow-up, and survival outcome*

Study	Year	Case	Control	Treatment regimen	Median follow-up (mo)	OS or DFS
Jung et al[9]	2010	134	107	6c CMF 6c FAC	109.8	OS, DFS
Swain et al[8]	2010	1,515 for DFS; 1,554 for OS	322 for DFS; 331 for OS	4c AC→4c T 4c AT 4c ACT	73	OS, DFS
Kil et al[10]	2006	59	101	6c CMF 4c AC 6c CAF	54	DFS
Gnant et al[11]	2006	328	195	6c CMF	120.6	OS, DFS
Colleoni et al[12]	2006	547	99	4c EC/AC→3c CMF	84	DFS
Vanhuyse et al[13]	2005	74	56	6c CMF 6c FEC 1c perioperative FAC	108	OS, DFS
Parulekar et al[14] (HR^+)	2005	187	68	6c CMF 6c CEF	105.6	OS, DFS
Parulekar et al[14] (HR^-)	2005	54	19	6c CMF 6c CEF	105.6	OS, DFS
Jonat et al[15]	2002	608	209	6c CMF	72	DFS
Pagani et al[16]	1998	736	460	3c-9c CMF	60	DFS
Bianco et al[17]	1991	166	55	3c-9c CMF	69	DFS
Goldhirsch et al[18]	1990	263	124	6c/7c CMF	48	DFS
Brincker et al[4]	1987	264	57	1 y cyclophosphamide	68	DFS
Brincker et al[4]	1987	238	77	1 y CMF	68	DFS
Ludwig Breast Cancer Study Group[19]	1985	340	59	12c CMF 12c CMF + prednisone	48	DFS

OS, overall survival; DFS, disease-free survival; c, cycle; CMF, cyclophosphamide/methotrexate/fluorouracil; FAC, fluorouracil/doxorubicin/cyclophosphamide; AC, doxorubicin/cyclophosphamide; T, docetaxel; AT, doxorubicin/docetaxel; ACT, doxorubicin/cyclophosphamide/docetaxel; CAF, cyclophosphamide/doxorubicin/fluorouracil; EC, epirubicin/cyclophosphamide; FEC, fluorouracil/epirubicin/cyclophosphamide; HR^+, hormone receptor–positive; CEF, cyclophosphamide/epirubicin/fluorouracil; HR^-, hormone receptor–negative.

2,331 cases and 776 controls were compared to analyze OS. The number of participants who were analyzed in the different studies varied from 54 to 1,515 in the CIA group and from 19 to 460 in the control group. Detailed characteristics of all enrolled studies are presented in Tables 1 and 2.

Disease-free survival

In the overall analysis, CIA was found to be a favorable factor for DFS (RR, 0.67; 95% CI, 0.61-0.74; $P < 0.001$; Fig. 1). Subgroup analysis for lymph nodes showed that participants with CIA had improved DFS compared with participants without CIA in the lymph node–positive subgroup (RR, 0.69; 95% CI, 0.61-0.77; $P < 0.001$) and the unclassified subgroup (RR, 0.65; 95% CI, 0.56-0.75; $P < 0.001$; Fig. 2A). In the subgroup analysis for ER status, participants with CIA had improved DFS compared with participants without CIA in the ER-positive subgroup (RR, 0.73; 95% CI, 0.61-0.88; $P = 0.001$) and the unclassified subgroup (RR, 0.63; 95% CI, 0.57-0.71; $P < 0.001$; Fig. 2B). However, there was no significant difference between participants with CIA and participants without CIA when ER status was negative (RR, 0.97; 95% CI, 0.66-1.41; $P = 0.858$; Fig. 2B). In the subgroup analysis for chemotherapy regimen, CIA was a beneficial factor for outcome among participants in all three subgroups: anthracycline (RR, 0.65; 95% CI, 0.54-0.79; $P < 0.001$), taxane (RR, 0.63; 95% CI, 0.52-0.76; $P < 0.001$), and nonanthracycline/nontaxane (RR, 0.70; 95% CI, 0.62-0.79; $P < 0.001$; Fig. 2C). Furthermore, for endocrine therapy, CIA played a beneficial role in DFS among participants undergoing endocrine therapy (RR, 0.65; 95% CI, 0.56-0.75; $P < 0.001$), among participants not undergoing endocrine therapy (RR, 0.62; 95% CI, 0.51-0.74; $P < 0.001$), and in the unclassified subgroup (RR, 0.69; 95% CI, 0.55-0.87; $P < 0.001$; Fig. 2D). In addition, our findings revealed that CIA is a beneficial factor for DFS among participants in both subgroups according to publication year (post-2000 subgroup: RR, 0.64; 95% CI, 0.57-0.72; $P < 0.001$; pre-2000 subgroup: RR, 0.67; 95% CI, 0.52-0.86; $P < 0.001$; Fig. 2E).

Overall survival

Of six enrolled cohorts, RRs for OS were available in five cohorts, and Kaplan-Meier curves were available in one cohort. The overall analysis showed that women who underwent CIA showed a significant improvement in OS compared with participants who did not undergo CIA (RR, 0.60; 95% CI, 0.50-0.72; $P < 0.001$; Fig. 3).

Publication bias and sensitivity analyses

According to the results of funnel plots and Egger's test, there was no publication bias in the overall meta-analysis of DFS (Supplemental Digital Content 1 and 2 illustrate the results of publication bias analysis; http://links.lww.com/MENO/A126) and OS (Supplemental Digital Content 3 and 4 illustrate the results of publication bias analysis; http://links.lww.com/MENO/A127). Sensitivity analyses also

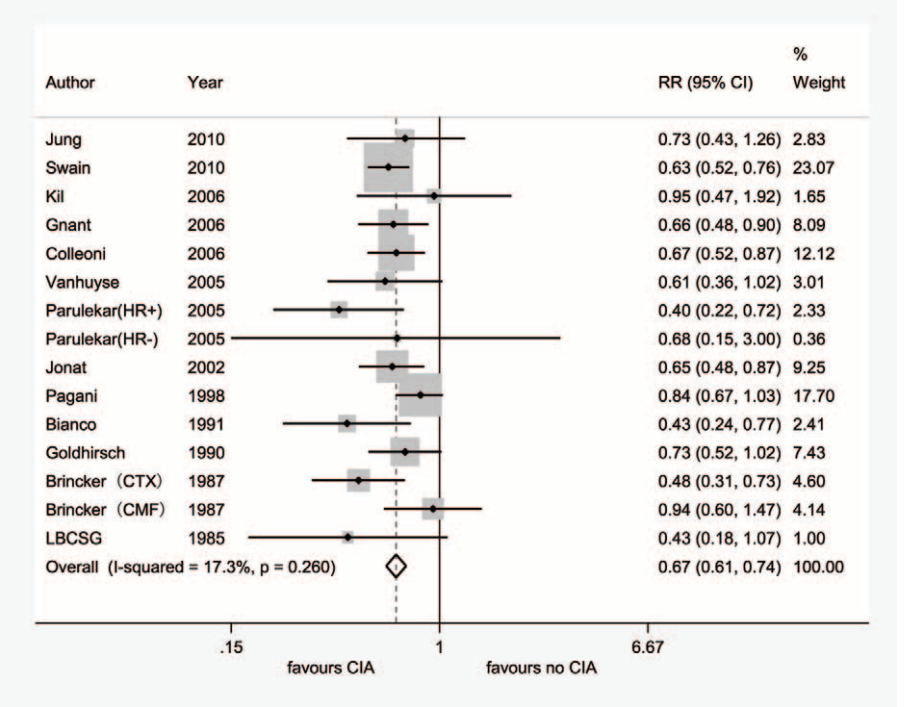

FIG. 1. Forest plot of relative risks (RRs) for the association of chemotherapy-induced amenorrhea (CIA) with disease-free survival in women with breast cancer. The size of the box is proportional to the weight that each study contributed to the meta-analysis. Overall estimates and CIs are marked by diamonds. Symbols to the right of the solid line indicate lnRRs greater than 0, and symbols to the left of the solid line indicate lnRRs less than 0. All combined RRs were calculated using the fixed-effects model. CTX, cyclophosphamide; CMF, cyclophosphamide/methotrexate/fluorouracil; HR^+, hormone receptor–positive; HR^-, hormone receptor–negative; LBCSG, Ludwig Breast Cancer Study Group.

showed that the overall RRs were not affected by any single study and that omission of any single study did not result in a significant difference (Supplemental Digital Content 5 illustrates the results of sensitivity analyses; http://links.lww.com/MENO/A128).

DISCUSSION

The association between CIA and breast cancer prognosis, being an important clinical issue, has been reported in many research articles; however, the results have been inconsistent. To the best of our knowledge, this is the first meta-analysis of published data that precisely and accurately addresses the prognostic role of CIA in breast cancer. The results showed that premenopausal women with breast cancer who underwent CIA exhibited significant improvements in DFS and OS compared with women who did not undergo CIA.

In this analysis, we found that CIA had beneficial effects on DFS and OS in women with breast cancer, especially for those with ER-positive tumors, whereas CIA had no significant effect on survival in women with ER-negative tumors. These results suggest that an indirect therapeutic effect of chemotherapy might occur in women with ER-positive tumors. However, for women with ER-negative tumors, chemotherapy might display a direct cytotoxic effect. Therefore, the superior outcome among women with CIA is most probably related to the combined effects of chemotherapy, including direct cytotoxic effect and indirect endocrine effect. Moreover, chemotherapy could result in permanent ovarian failure, although this is not inevitable. Thus, the actual mechanism underlying the effect of CIA on breast cancer remains obscure. Furthermore, as another important treatment for breast cancer, endocrine therapy can also lead to chemical castration and might play a role in the indirect endocrine effect of CIA on women with breast cancer. Unfortunately, our analysis showed that CIA was a beneficial factor for breast cancer prognosis regardless of whether women had undergone endocrine therapy. However, in some studies, women with ER-positive or hormone receptor–positive breast cancer only received endocrine therapy consisting of tamoxifen for 5 years,[9,12] whereas the details of endocrine therapy were not precisely described in other studies.[4,10,16-19] As a result, we could not assess the effect of aromatase inhibitors on the prognostic role of CIA in premenopausal breast cancer. Indeed, further studies are needed to reveal the relationship between the mechanisms of chemotherapy and endocrine therapy and their roles in breast cancer prognosis.

Data from many studies have shown that CIA is less likely to occur in younger women.[15-18,21-24] Although our study did not show a definite association between the effect of CIA and the age of participants, some studies have suggested that CIA primarily has favorable effects on younger women.[4,19] Therefore, for young premenopausal women with ER-positive high-risk breast cancer (characterized by high histopathologic grade or HER2 receptor positivity) who do not develop CIA, further treatments to inhibit ovarian function (such as ovarian ablation) may improve prognosis.

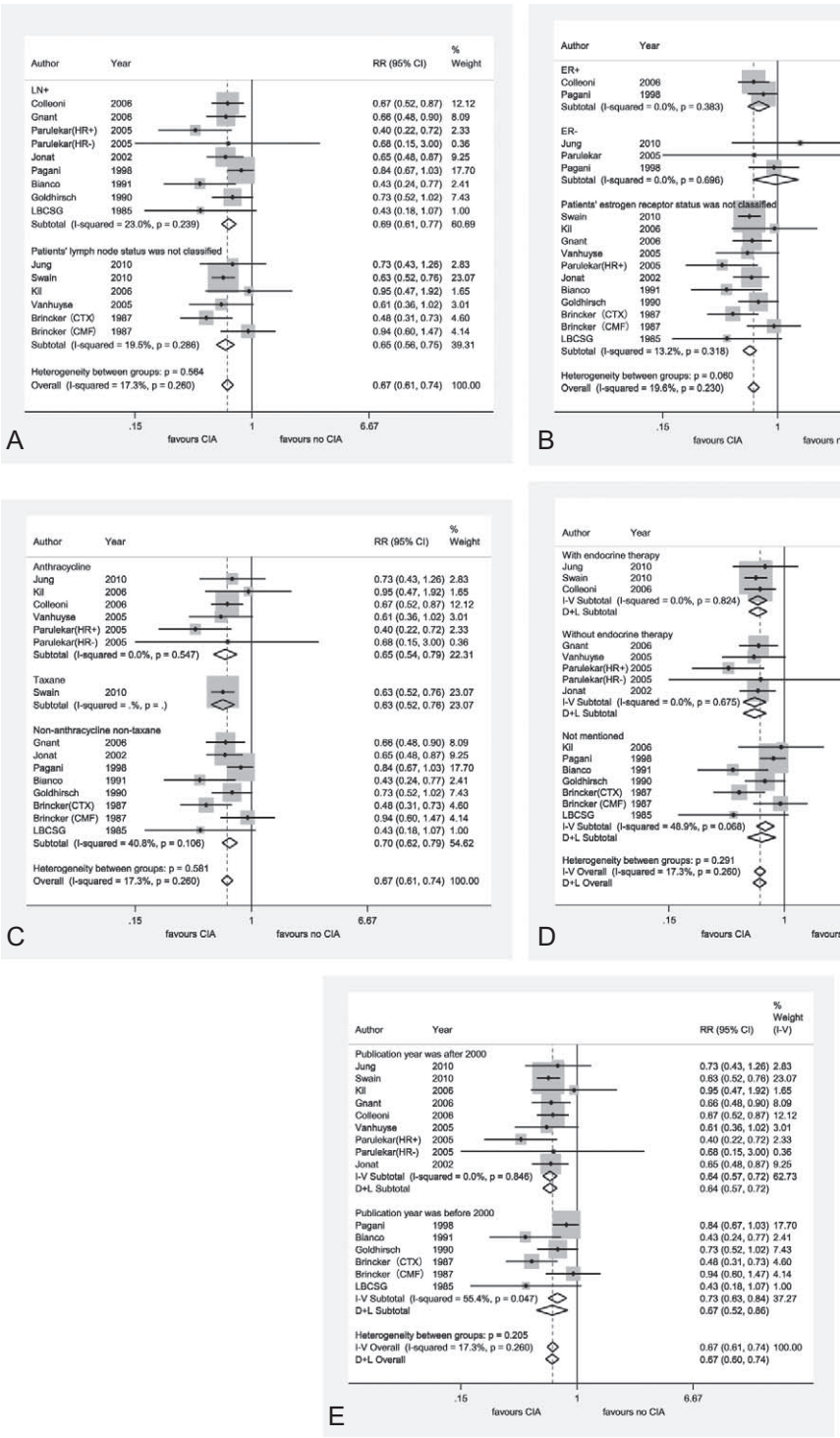

FIG. 2. Forest plot of relative risks (RRs) for disease-free survival in subgroup analyses of (**A**) lymph node with the fixed-effects model, (**B**) estrogen receptor with the fixed-effects model, (**C**) chemotherapy regimen with the fixed-effects model, (**D**) endocrine therapy with the fixed-effects and random-effects models, and (**E**) publication year with the fixed-effects and random-effects models. The size of the box is proportional to the weight that each study contributed to the meta-analysis. Overall estimates and CIs are marked by diamonds. Symbols to the right of the solid line indicate RRs greater than 1, and symbols to the left of the solid line indicate RRs less than 1. When $P < 0.1$ or I^2 was higher than 50%, heterogeneity was considered to exist. RRs were calculated with the DerSimonian-Laird method (D + L; random-effects method); otherwise, inverse-variance method (I-V; fixed-effects method) was applied. These two methods provided similar results. LN^+, lymph node–positive; HR^+, estrogen receptor–positive and/or progesterone receptor–positive; HR^-, estrogen receptor–negative and/or progesterone receptor–negative; LBCSG, Ludwig Breast Cancer Study Group; CTX, cyclophosphamide; CMF, cyclophosphamide/methotrexate/fluorouracil; CIA, chemotherapy-induced amenorrhea; ER^+, estrogen receptor–positive; ER^-, estrogen receptor–negative.

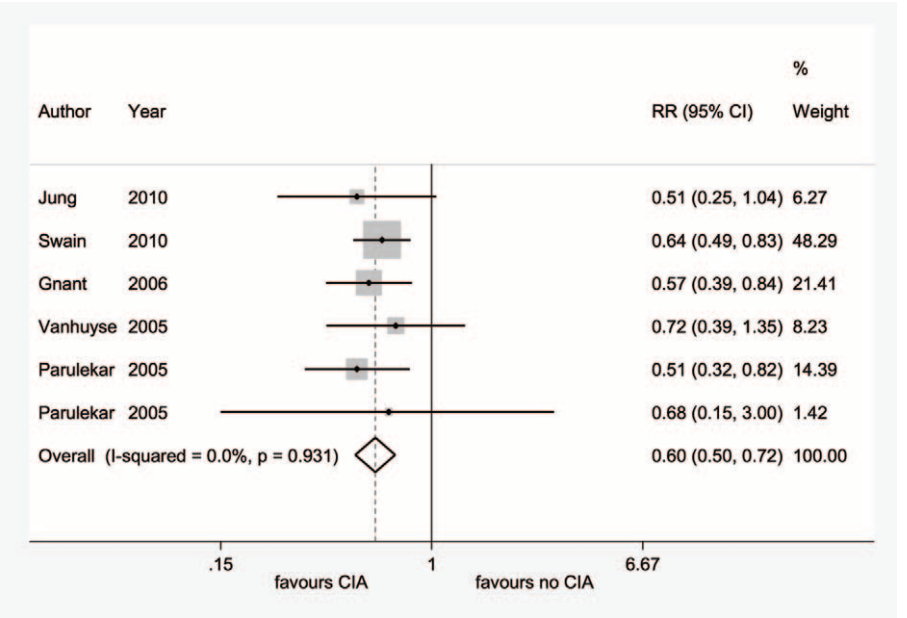

FIG. 3. Forest plot of relative risks (RRs) for overall survival for the association of chemotherapy-induced amenorrhea (CIA) with breast cancer outcome. The size of the box is proportional to the weight that each study contributed to the meta-analysis. Overall estimates and CIs are marked by diamonds. Symbols to the right of the solid line indicate RRs greater than 1, and symbols to the left of the solid line indicate RRs less than 1.

This meta-analysis has some limitations. First, because of the lack of sufficient data in most of the included articles, it was not possible to investigate whether there were associations between CIA, tumor size, and HER2/ERBB2 status in this meta-analysis. Second, the current follow-up data from one trial were reported only in conference abstracts; therefore, extracting a complete detailed dataset for this analysis would be difficult until it is published in a peer-reviewed journal.[11] Finally, there was a discrepancy in the definitions of CIA with respect to timing of onset and duration. Because amenorrhea may occur at any time after the start of chemotherapy, amenorrhea status might have been incorrectly designated. For example, women who relapsed very early might have been misclassified as nonamenorrheic because their follow-up was too short and their amenorrhea had not yet developed. Any of these limitations might affect the final results to varying degrees.

Although the results of our study and many other studies demonstrate that CIA plays a prognostic role in chemotherapy-treated premenopausal breast cancer, the actual mechanism between clinical outcomes and CIA is far from clear, and further studies are needed.

CONCLUSIONS

CIA might be a reliable marker for predicting prognosis in premenopausal women with ER-positive breast cancer who are undergoing adjuvant chemotherapy. This beneficial effect of CIA on breast cancer does not seem to vary widely by lymph node status, chemotherapy regimen, or endocrine therapy. However, additional studies are needed to establish the exact role of CIA in breast cancer.

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