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ORIGINAL ARTICLE

Endocrine Therapy for Ductal Carcinoma In Situ (DCIS) of the Breast with Breast Conserving Surgery (BCS) and Radiotherapy (RT): a Meta-Analysis

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Abstract

The management of ductal carcinoma in situ (DCIS) with endocrine therapy remains controversial. A meta-analysis was conducted to evaluate the role of endocrine therapy for DCIS with breast conserving surgery (BCS) and radiotherapy (RT). A total of 7 articles with randomized controlled trials were included. Five articles compared the effects of BCS and RT followed by tamoxifen (TAM) or not (BCS + RT + TAM vs BCS + RT) and 2 compared the effects of TAM and anastrozole (ANA). TAM obviously reduced the rates of recurrence of ipsilateral breast cancer (IBCR), recurrence of contralateral breast cancer (CBCR), recurrence of ipsilateral invasive breast cancer (IBCR-INV) and recurrence of contralateral DCIS (CBCR-DCIS), and increased the rate of event-free survival (EFS). While ANA reduced the rates of CBCR and recurrence of contralateral invasive breast cancer (CBCR-INV). Patients with ANA had higher incidence of arthralgia, osteoporosis, hypercholesteremia, headache and vaginal dryness, but lower incidence of deep-vein thrombosis, pulmonary embolism, vasomotor or gynaecological, hot flushes, vaginal haemorrhage, vaginal discharge and vaginal candidiasis than TAM. In conclusion, DCIS patients with positive hormone receptors should be recommended to receive endocrine therapy. Selection of TAM or ANA is based on clinical characteristics and underlying disease of patients, as well as the side-effects of drugs.

Keywords Ductal carcinoma in situ (DCIS) · Endocrine therapy · Meta-analysis

Introduction

Based on the development of mammography screening and early diagnosis, ductal carcinoma in situ (DCIS) has been accurately detected and attracting attention [1, 2]. American Cancer Society showed that about 1600 new cases of female carcinoma in situ were diagnosed in 2016, which accounted for 25% of new female breast cancer [3].

Breast conserving surgery (BCS), radiation therapy (RT), and endocrine therapy have been recognized as the standard of DCIS treatments [4, 5]. A meta-analysis by H. Staley [6] showed that regardless of hormone receptor status and whether RT was received or not, BCS followed by TAM reduced the risk of local recurrence of ipsilateral invasive breast cancer (IBCR-INV) ($RR = 0.79$,95% $CI = 0.62–1.01$), recurrence of ipsilateral DCIS (IBCR-DCIS) ($RR = 0.75$), recurrence of contralateral invasive breast cancer (CBCR-INV) ($RR = 0.57$), and recurrence of contralateral DCIS (CBCR-DCIS) ($RR = 0.50$), but did not reduce the mortality ($RR = 1.11$). However, it was noticed that not all the cases in the UK/ANZ trial [7, 8], which was included in the meta-analysis of H. Staley [6], received completely random allocation. It may produce unreliable results. Moreover, for postmenopausal women with invasion breast cancer (IBC), Anastrozole (ANA) has higher disease free survival (DFS), tolerance and safety than TAM, while there was no statistic difference

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between the two drugs [9–11]. It is still unknown whether the two drugs have the same clinical effects on postmenopausal women with DCIS. The National Comprehensive Cancer Network (NCCN) guideline recommends that TAM and aromatase inhibitors (AIs) can be used for postmenopausal DCIS patients [12]. Two large relevant clinical trials had compared the treatment efficacy and side effects of different endocrine therapeutic drugs (TAM vs. ANA) on postmenopausal DCIS patients [13, 14]. Therefore, in light of the issues above, we made a meta-analysis to evaluate the effect of endocrine therapy of women with DCIS after BCS and RT.

Materials and Methods

Search Strategy

Without restriction of language, PubMed, Cochrane Library, and Web of Science were searched until June 30, 2017. The search terms used were "ductal carcinoma in situ" or "breast cancer" and "adjuvant radiotherapy" and "breast conserving surgery" or "lumpectomy" or "quadrantectomy" or "segment mastectomy" and "Randomized Controlled Trial" or "clinical trial". All references in the identified articles well retrieved by manual searching to ensure that all of related studies were included.

Inclusion Criteria

All trials in eligible studies were RCTs.

All trials focused on the therapy of DCIS, including BCS, RT, and endocrine therapy.

All trials provided sufficient data, including recurrence of ipsilateral breast cancer (IBCR), recurrence of contralateral breast cancer (CBCR), distant metastases, event-free survival (EFS), mortality, etc.

Literature Quality Evaluation and Data Extraction

Four investigators independently extracted and analyzed the data and conducted the quality assessment of eligible studies with Consolidated Standards of Reporting Trials (CONSORT) statement [15]. When encountering contradiction, the investigators reassessed the data until achieving consensus. The information collected from eligible studies were: the first author's name, year of publication, name of the RCTs, population characteristics (median age, detected method, and pathological type of breast cancer), median follow-up time, treatments of the cases and controls, and numbers of cases and controls.

Statistical Analysis

Review Manager 5.3 software was used to perform the Meta-analysis. Heterogeneity among the trials was assessed by Cochran's Q test and quantified by I^2 statistic. When there was no clinical or statistical heterogeneity among eligible studies ($P \geq 0.1$, $I^2 \leq 50\%$), fixed effects model was used, otherwise, random effects model was used [16]. Risk ratios (*RRs*) and 95% confidential intervals (*CIs*) were calculated by *Z*-test to assess the associations between different treatments and clinical effects. $P < 0.05$ was considered statistically significance. Publication bias was tested using funnel plots if the number of included studies was not less than 5.

Results

Results of Search Strategy

Figure 1 presents the process of the studies selection. A total of 2265 articles were searched from PubMed, Cochrane Library, and Web of Science by using the terms mentioned before. 1502 articles were left after removing duplicates. 1421 articles were excluded because therapy for DCIS was not mentioned. Then 36 articles which were no RCTs and 38 articles which were merely the registration information on Cochrane library or did not provide enough data about TAM and ANA were excluded. Ultimately, only 7 articles were included in this meta-analysis. Literature quality was conducted according by CONSORT statements (Table 1).

Study Characteristics

The characteristic of the eligible studies in meta-analysis was listed in Tables 2 and 3. Five articles [7, 8, 17–19] were related to the comparison between the "BCS + RT + TAM" group and the "BCS + RT" group. And two articles [13, 14] were related to the comparison between two endocrine drugs, ANA and TAM.

Meta-Analysis Data

Meta-analysis was divided different into 2 parts according to the treatment methods comparison and different follow-up times.

Comparison between "BCS + RT + TAM" Group and "BCS + RT" Group

In the meta-analysis 5 articles [7, 8, 17–19] reported 2 RCTs (including NSABP B-24 and UK/ANZ trial) which enrolled 2322 DCIS patients without ER and PR status, 1171 patients were enrolled "BCS + RT + TAM" group and 1151 were

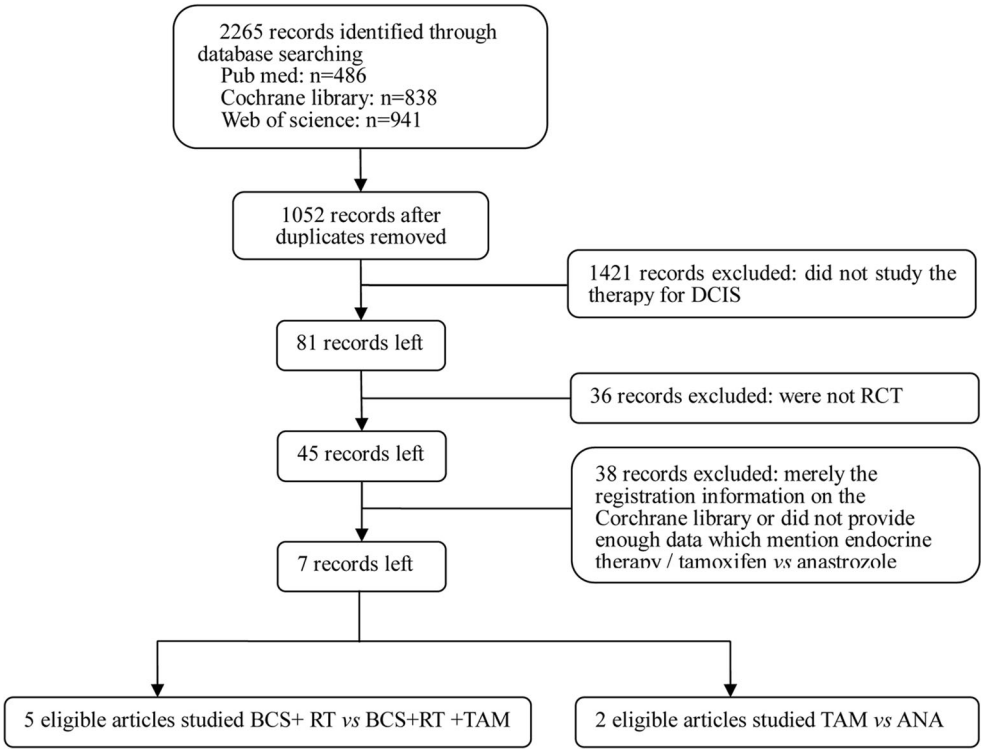

Fig. 1 Flow chart of study selection. Abbreviation: ANA: anastrozole; BCS: breast conserving surgery; RT: radiotherapy; TAM: tamoxifen. * 3 eligible articles studied both BCS + RT vs BCS and BCS + RT + TAM vs BCS + RT

submitted to "BCS + RT" group. According to different median follow-up times, these articles were divided into 2 subgroups: group "<10 years" [7, 18] and group ">10 years" [8, 19]. (Fig. 2a-j).

IBCR, IBCR-INV and IBCR-DCIS

IBCR, IBCR-INV and IBCR-DCIS were all mentioned in these 4 articles [7, 8, 18, 19]. Fixed effects models were used because of low heterogeneity (I^2 < 50%). TAM reduced the rates of IBCR during 2 different median follow-up times and decreased the rates of IBCR-INV for less than 10 years median follow-up times (① IBCR: group "<10 years" P = 0.03, RR = 0.75, 95% CI = 0.57–0.98; group ">10 years" P = 0.04, RR = 0.80, 95% CI = 0.65–0.99. ② IBCR-INV: group "<10 years" P = 0.03, RR = 0.63, 95% CI = 0.41–0.95). However, there was no statistical difference between group "BCS + RT+TAM" and "BCS + RT" group in the rates of IBCR-INV for more than 10 years median follow-up time and the rates of IBCR-DCIS during 2 different median follow-up times (① IBCR-INV: group ">10 years" P = 0.08, RR = 0.74, 95% CI = 0.56–1.03. ② IBCR-DCIS: group "<10 years" P = 0.41, RR = 0.86, 95% CI = 0.60–1.23; group ">10 years" P = 0.32, RR = 0.85, 95% CI = 0.63–1.16) (Fig. 2 a-c).

CBCR, CBCR-INV and CBCR-DCIS

All the 4 articles [7, 8, 18, 19] reported CBCR, CBCR-INV and CBCR-DCIS of two different median follow-up times, and fixed effects models were used (I^2 = 0%). Comparing to BCS followed by RT, BCS followed by RT and TAM reduced the rates of CBCR during 2 different median follow-up times and the rates of CBCR-INV for less than 10 years median follow-up times (① CBCR: group "<10 years" P = 0.02, RR = 0.59, 95% CI = 0.38–0.93; group ">10 years" P = 0.009, RR = 0.64, 95% CI = 0.46–0.89. ② CBCR-DCIS: group "<10 years" P = 0.03, RR = 0.33, 95% CI = 0.12–0.91). There was no statistical difference between "BCS + RT+TAM" group and "BCS + RT" group in the rates of CBCR-DCIS for more than 10 years median follow-up time and the rates of IBCR-DCIS during 2 different median follow-up times (① CBCR-DCIS: group ">10 years" P = 0.09, RR = 0.59, 95% CI = 0.31–1.09. ② CBCR-INV: group "<10 years" P = 0.18, RR = 0.71, 95% CI = 0.42–1.17; group ">10 years" P = 0.06, RR = 0.67, 95% CI = 0.44–1.02) (Fig. 2 d-f).

Other Data

Two articles [18, 19] described the NSABP B-24 trial in two different median follow-up times and reported the following data. For less than or more than 10 years median follow up, TAM significantly increased the rates of EFS (group ">10 years" P = 0.003, RR = 1.07, 95% CI = 1.02–1.12; group ">10 years" P = 0.006, RR = 1.10, 95% CI = 1.03–1.18) (Fig. 2 g).

For the rates of mortality, Non-BC death, BC death, local, regional, and distant recurrence, and occurrence of endometrial cancer, however, TAM did not show the statistical difference compared to postoperative RT only (① group "<10 years":

Table 1 Quality evaluation result of 15 eligible articles by Consolidated Standards of Reporting Trials (CONSORT) Statement (2010)[15]

Section/Topic	Item Number	Checklist Item	Number	Percentage (%)
Title and abstract	1a	Identification as a randomized trial in the title	6[7,8,13,14,17,19]	85.71
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts)	6[7,8,13,14,17,19]	85.71
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	7[7,8,13,14,17–19]	100
	2b	Specific objectives or hypotheses	7[7,8,13,14,17–19]	100
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial), including allocation ratio	6[7,8,13,14,17,19]	85.71
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	2[7,17]	28.57
Participants	4a	Eligibility criteria for participants	7[7,8,13,14,17–19]	100
	4b	Settings and locations where the data were collected	2[7,17]	28.57
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7[7,8,13,14,17–19]	100
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	6[7,8,13,14,17,19]	85.71
	6b	Any changes to trial outcomes after the trial commenced, with reasons	1[8]	14.29
Sample size	7a	How sample size was determined	3[7,13,14]	42.86
	7b	When applicable, explanation of any interim analyses and stopping guidelines	0	0
Randomization Sequence generation	8a	Method used to generate the random allocation sequence	4[7,8,13,14]	57.14
	8b	Type of randomization; details of any restriction (such as blocking and block size)	4[7,8,13,14]	57.14
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5[7,8,13,14,17]	46.67
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	0	0
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	3[13,14,17]	42.86
	11b	If relevant, description of the similarity of interventions	2[13,14]	28.57
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7[7,8,13,14,17–19]	100
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	5[8,13,14,17,19]	71.43
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	6[7,8,13,14,17,18]	85.71
	13b	For each group, losses and exclusions after randomization, together with reasons	6[7,8,13,14,17,18]	85.71
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6[7,8,13,14,17,18]	85.71
	14b	Why the trial ended or was stopped	0	0
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	7[7,8,13,14,17–19]	100
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7[7,8,13,14,17–19]	100
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	7[7,8,13,14,17–19]	100
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	7[7,8,13,14,17–19]	100
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	1[8]	14.29
Harms	19	All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms	3[13,14,17]	42.86
Discussion				

Table 1 (continued)

Section/Topic	Item Number	Checklist Item	Number	Percentage (%)
Limitations	20	Trial limitations; addressing sources of potential bias; imprecision; and, if relevant, multiplicity of analyses	2[14,19]	28.57
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	0	0
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	7[7,8,13,14,17–19]	100
Other information				
Registration	23	Registration number and name of trial registry	4[8,13,14,19]	57.14
Protocol	24	Where the full trial protocol can be accessed, if available	0	0
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	7[7,8,13,14,17–19]	100

Mortality $P = 0.83$, $RR = 0.96$, 95% $CI = 0.63–1.44$;Non-BC death $P = 0.90$, $RR = 0.97$, 95% $CI = 0.60–1.56$;BC death $P = 0.20$, $RR = 0.50$, 95% $CI = 0.17–1.46$; Local, regional, and distant recurrence $P = 0.15$, $RR = 0.38$, 95% $CI = 0.10–1.41$; Endometrial cancer $P = 0.22$, $RR = 2.34$, 95% $CI = 0.61–9.00$. ② group ">10 years": Local, regional, and distant recurrence $P = 0.47$, $RR = 0.70$, 95% $CI = 0.27–1.83$) (Fig. 2 h-j).

Comparison between "ANA" Group and "TAM" Group for Postmenopausal DCIS

In the meta- analysis, two RCTs, NSABP B-35 trial [13] and IBIS-II DCIS trial [14], enrolled 6015 postmenopausal women with DCIS and positive estrogen and progesterone receptor. All patients were divided into "ANA" group ($n = 2988$) and "TAM" group ($n = 3027$) randomly (Fig. 3).

IBCR, IBCR-INV and IBCR-DCIS

Two articles [13, 14] all reported IBCR, IBCR-INV and IBCR-DCIS, and fixed effects models were used because of no heterogeneity ($I^2 = 0\%$). There was no statistical difference between group "ANA" and group "TAM" of these data. (① IBCR: $P = 0.38$, $RR = 0.88$, 95% $CI = 0.66–1.17$; ② IBCR-INV: $P = 0.47$, $RR = 0.85$, 95% $CI = 0.55–1.32$; ③ IBCR-DCIS: $P = 0.60$, $RR = 0.90$, 95% $CI = 0.62–1.32$) (Fig. 3 a).

Table 2 Characteristics of studies of comparison between "BCS + RT + TAM" group and "BCS + RT" group

Trial	NSABP B-24	UK/ANZ
Date	May, 1991-Apr, 1994	May, 1990- Aug, 1998
Population Characteristics:		
Median age	NM	NM
Detected method	Physical examination, mammography, or both	Breast screening programme
Pathological type of breast cancer	DCIS and DCIS+LCIS	DCIS
Therapy:		
Surgery	BCS, tumor-free margins after BCS, tumor-negative axillary nodes	BCS, tumor-free margins after BCS
Radiotherapy	50Gy/25 fraction	50Gy/25 fraction
Tamoxifen	20 mg /day for 5 years	20 mg /day for 5 years
Patients Randomized		
Total	1799	523
BCS + RT + TAM	899	272
BCS + RT	900	251
Median follow-up	13.5 years	12.7 years
Related articles:		
Author-published year (Median follow-up)	Fisher B-1999[17] (6 years); Fisher B-2001[18] (6.9 years); Irene L-2011[19] (13.5 years);	Houghton J-2003[7] (4.3 years); Cuzick J-2011[8] (12.7 years)

Abbreviations: *BCS* breast conserving surgery, *DCIS* ductal carcinoma in suit, *LCIS* lobular carcinoma in situ, *NM* not mentioned, *RT* radiotherapy, *TAM* tamoxifen

Table 3 Characteristics of studies of comparison between "ANA" group and "TAM" group for postmenopausal DCIS

Trial	IBIS-II DCIS	NSABP B-35
Date	Mar, 2003- Feb, 2012	Jan, 2003- Jun, 2006
Population Characteristics:	Postmenopausal women Median age was 60.3 years DCIS or DCIS+LCIS ER (+) or PR (+);	Postmenopausal women DCIS or DCIS+LCIS ER (+) or PR (+);
Therapy:		
ANA	1 mg /day for 5 years	1 mg /day for 5 years
TAM	20 mg /day for 5 years	20 mg /day for 5 years
Patients Randomized		
Total	2938	3077
ANA	1449	1539
TAM	1489	1538
Median follow-up	7.2 years	9.0 years
Related articles:		
Author-published year (Median follow-up)	Forbes FJ −2015[14] (7.2 years)	Margolese RG-2015[13] (9.0 years);

Abbreviations: *ANA* anastrozole, *DCIS* ductal carcinoma in suit, *ER* estrogen receptor, *LCIS* lobular carcinoma in situ, *PR* progesterone receptor, *TAM* tamoxifen

CBCR, CBCR-INV and CBCR-DCIS

All the 2 articles [13, 14] reported CBCR, CBCR-INV and CBCR-DCIS, and fixed effects models were used ($I^2 < 50\%$). Compared to TAM, ANA reduced the rates of CBCR and CBCR-INV, however, there was no difference between the two groups for CBCR-DCIS (① CBCR: $P = 0.03$, $RR = 0.71$, 95% $CI = 0.52–0.97$; ② CBCR-INV: $P = 0.009$, $RR = 0.59$, 95% $CI = 0.40–0.88$; ③ CBCR-DCIS: $P = 0.98$, $RR = 1.01$, 95% $CI = 0.59–1.73$) (Fig. 3 b).

Mortality, Non-BC Death, and BC Death

Two articles [13, 14] all described the rates of mortality, Non-BC death, and BC death, and fixed effect models were used for low heterogeneities ($I^2 = 0\%$). There was no statistical difference between group "ANA" and group "TAM" of the three data (① Mortality: $P = 0.61$, RR = 1.06, 95% CI = 0.84–1.35; ② Non-BC death: $P = 0.39$, RR = 1.11, 95% CI = 0.87–1.43; ③ BC death: $P = 0.24$, RR = 0.55, 95% CI = 0.20–1.48) (Fig. 3 c) .

Non-breast Secondary Primary Caner, Uterine Cancer and Non-gynecological Cancer

Two studies [13, 14] all described the rate of non-breast secondary primary caner, uterine cancer and non-gynecological cancer (such as lung cancer, gastrointestinal cancer, and lymphoma etc.). For non-breast secondary primary caner and non-gynecological cancer, fixed effect model was used ($I^2 = 0\%$), and for uterine cancer, random effect model was used ($I^2 = 59\%$). It was reported that there was no statistical difference between group "ANA" and group "TAM" for these 3 data (① Non-breast secondary primary caner: $P = 0.86$, $RR = 0.98$, 95% $CI = 0.80–1.21$; ② Uterine cancer: $P = 0.11$, $RR = 0.26$, 95% $CI = 0.05–1.34$; ③ Non-gynecological cancer: $P = 0.30$, $RR = 1.13$, 95% $CI = 0.90–1.41$) (Fig. 3 d).

Advantages and Disadvantages

Two studies [13, 14] all reported the bone and joint disease and thrombosis. The incidence of arthralgia of patients with ANA was 1.28 times compared to patients with TAM and the incidence of osteoporosis of patients with ANA was 1.61 times compared to patients with TAM. But for thrombosis, ANA showed obvious advantages in both deep-vein thrombosis and pulmonary embolism compared to TAM (① Arthralgia: $P = 0.009$, $RR = 1.28$, 95% $CI = 1.06–1.53$; ② Osteoporosis: $P = 0.001$, $RR = 1.61$, 95% $CI = 1.21–2.14$); ③ Deep-vein thrombosis: $P = 0.002$, $RR = 0.16$, 95% $CI = 0.05–0.53$; ④ Pulmonary embolism: $P < 0.00001$, $RR = 0.88$, 95% $CI = 0.83–0.92$) (Fig. 3 e).

Other data as follows were reported by IBIS-II DCIS trial [14]. The incidences of vaginal dryness, hypercholesteremia, and headache of patients with ANA were higher than that of patients with TAM, and the incidences of vasomotor or gynaecological, hot flushes, vaginal haemorrhage, vaginal discharge, and vaginal candidiasis of patients with ANA were lower than that of patients with TAM (① Vaginal dryness: $P = 0.05$; $RR = 1.22$; 95% $CI = 1.00–1.49$; ② Hypercholesteremia: $P<0.0001$; $RR = 4.02$; 95% $CI = 2.08–7.76$; ③ Headache: $P = 0.05$; $RR = 1.38$; 95% $CI = 1.00–1.91$; ④ Vasomotor or gynaecological: $P<0.00001$; $RR = 0.88$; 95%

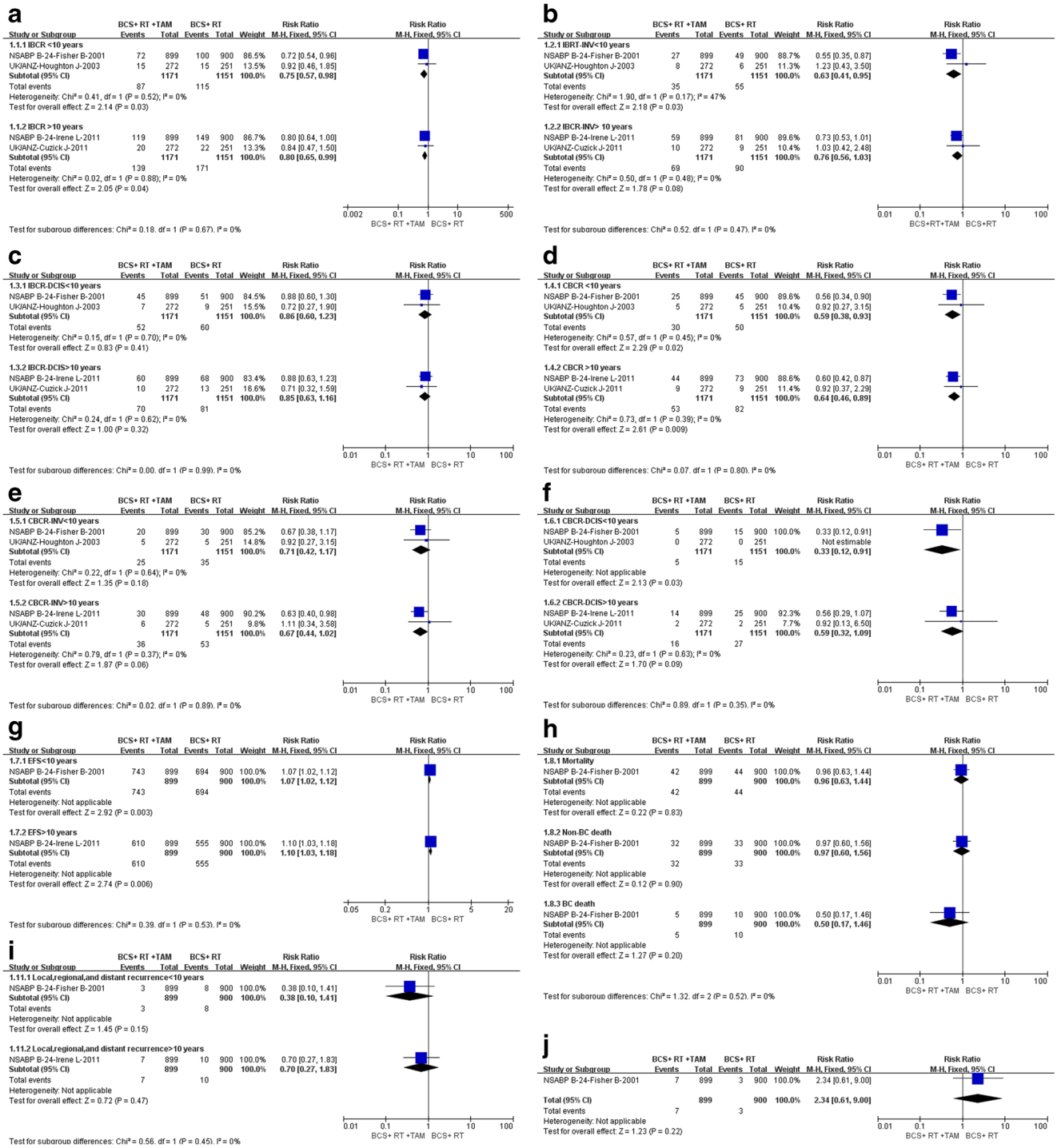

Fig. 2 Forest plots showing meta-analysis of comparison between "BCS + RT+ TAM" group and "BCS + RT" group for DCIS in different follow up times. Different outcomes were shown from a to j. Abbreviation: BCS: breast conserving surgery; BC: breast cancer; BC death: breast cancer related death; CBCR: recurrence of contralateral breast cancer; CBCR-INV: recurrence of contralateral invasive breast cancer; CBCR-DCIS: recurrence of contralateral DCIS; *CI:* confidential interval; DCIS: ductal carcinoma in suit; EFS: event-free survival; I^2: Heterogeneity; IBCR: recurrence of ipsilateral breast cancer; IBCR-INV: recurrence of ipsilateral invasive breast cancer; IBCR-DCIS: recurrence of ipsilateral DCIS; Non-BC death: non-breast cancer related death; *RR*: risk ratio; RT: radiotherapy; TAM: tamoxifen

CI = 0.83–0.92;⑤ Hot flushes:*P* = 0.03; *RR* = 0.94; 95% *CI* = 0.88–0.99;⑥ Vaginal haemorrhage:*P*<0.0001; *RR* = 0.45; 95% *CI* = 0.30–0.66;⑦ Vaginal discharge:*P*<0.00001; *RR* = 0.23; 95% *CI* = 0.15–0.33;⑧ Vaginal candidiasis:*P*<0.0001; *RR* = 0.20; 95% *CI* = 0.09, 0.42). However, there was no statistical difference between group

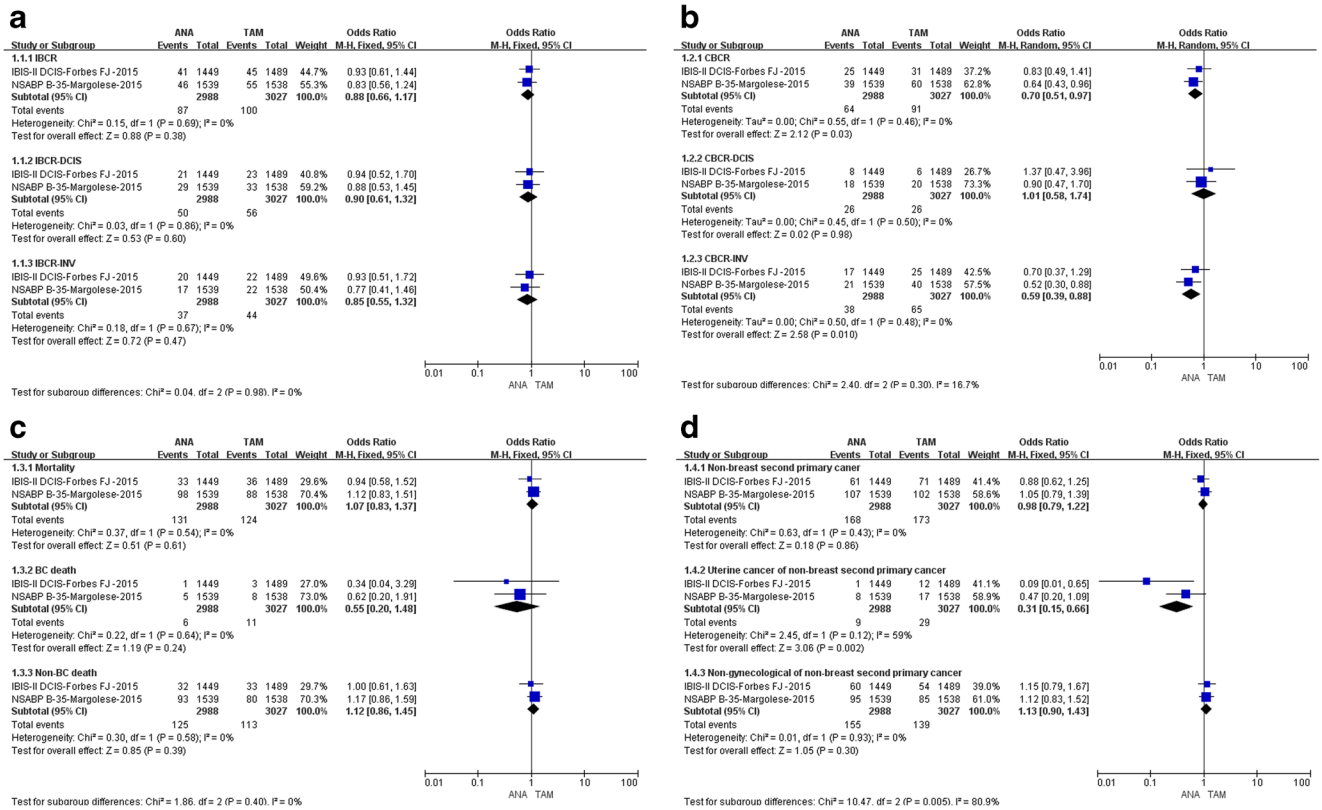

Fig. 3 Forest plots showing meta-analysis of comparison between "ANA" group and "TAM" group for postmenopausa DCIS. Different outcomes were shown from a to d. Abbreviation: ANA: anastrozole; BCS: breast conserving surgery; BC: breast cancer; BC death: breast cancer related death; CBCR: recurrence of contralateral breast cancer; CBCR-INV: recurrence of contralateral invasive breast cancer; CBCR-DCIS: recurrence of contralateral DCIS; *CI:* confidential interval; DCIS: ductal carcinoma in suit; I^2: Heterogeneity; IBCR: recurrence of ipsilateral breast cancer; IBCR-INV: recurrence of ipsilateral invasive breast cancer; IBCR-DCIS: recurrence of ipsilateral DCIS; Non-BC death: non-breast cancer related death; *RR*: risk ratio; RT: radiotherapy; TAM: tamoxifen

"ANA" and group "TAM" for the incidences of cardiovascular eye disease (① Cardiovascular:$P = 0.38$; $RR = 1.14$; 95% $CI = 0.85–1.51$;② Eye disease:$P = 0.16$; $RR = 1.13$; 95% $CI = 0.95–1.34$) (Fig. 3 e).

Discussion

The incidence of DCIS increases year by year based on the remarkable development of mammography screening and early diagnosis. According to the latest data from American Cancer Society, cases of newly diagnosed DCIS in 2016 accounts for 25% of all new cases of breast cancer diagnoses in women [3]. The integrated treatment including BCS, RT and endocrine therapy has been the main treatment for DCIS [12]. However, at present there have not yet searched adequate number of RCTs about the treatments of DCIS, especially about whether endocrine drug is appropriate or efficient. Therefore, a meta-analysis was conducted to help clinical doctors find the keys of the treatments of DCIS.

UK/ANZ trial [7, 8] and the NSABP B-24 trial [17, 19] discussed the role of TAM in the treatment of DCIS. Our meta-analysis confirmed that regardless of the hormonal-receptor status, TAM remarkably reduced the IBCR, IBCR-INV less than 10 years, CBCR and CBCR-DCIS less than 10 years, and increased the rate of EFS. However, there was no statistical difference between "BCS + RT + TAM" group and "BCS + RT" group for the rates of IBCR-DCIS, IBCR-INV more than 10 years, CBCR-INV, and CBCR-DCIS more than 10 years, mortality, distant metastases, and occurrence of endometrial cancer. The limitation of our meta-analysis was that there was no evaluation of estrogen and progesterone receptor (ER and PR) status in these two trials. While these results in Staley's meta-analysis were opposite [6]. Through carefully comparison, we found that Staley's meta-analysis [6] ignored the influence of postoperative RT on treatment effects and data of UK/ANZ trial [7, 8] were not all from completely random allocation. Therefore, we can conclude that our results were more reliable.

ER and PR negativity were both associated with comedo necrosis and high nuclear grade which showed poor prognosis of DCIS [20, 21]. Comedo necrosis and nuclear grade, however, cannot replace hormone status to determine endocrine therapy for DCIS [20]. A sub-study derived from NSABP B-24 confirmed that adjuvant TAM

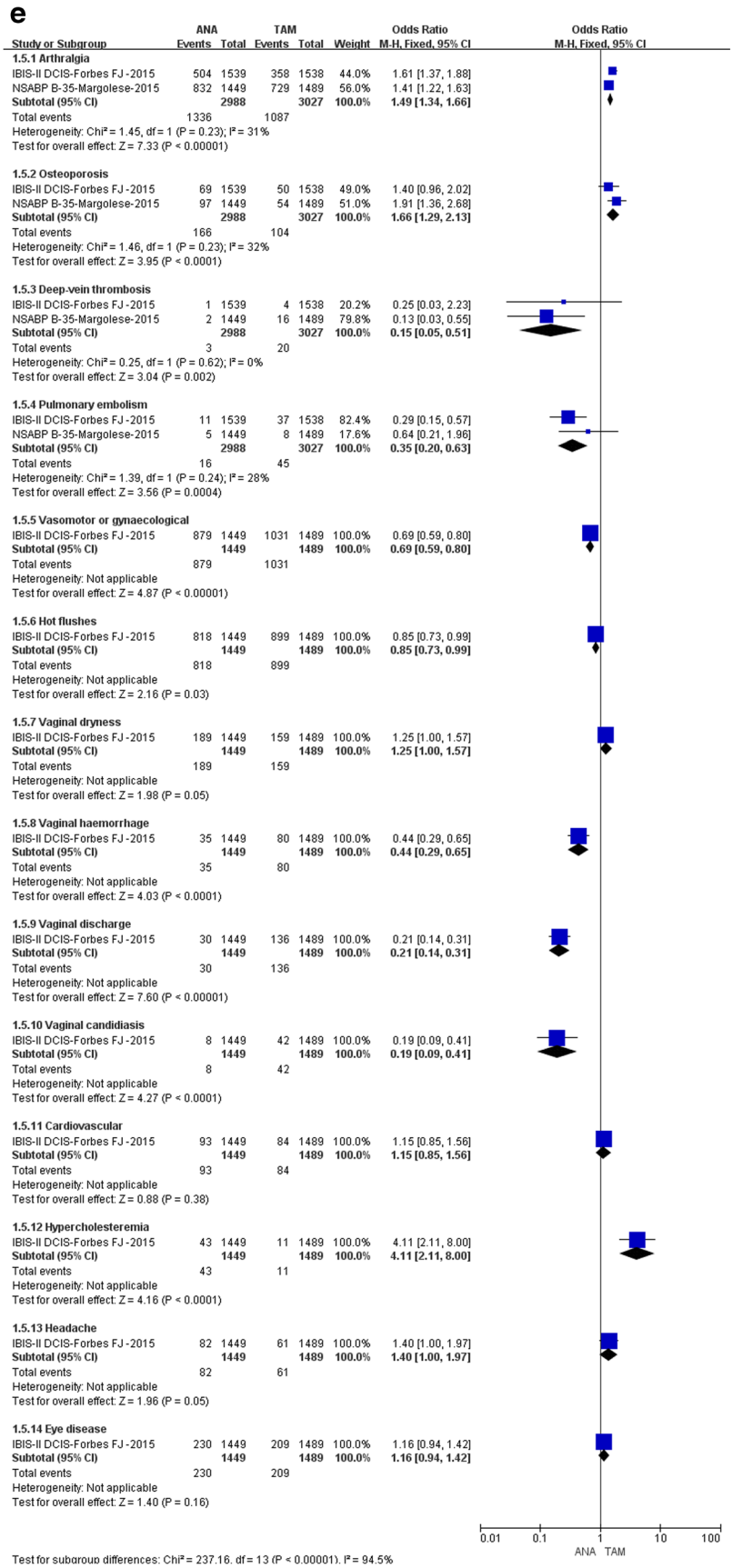

Fig. 3 continued.

significantly reduced the rate of breast cancer recurrence of DCIS patients with positive hormone receptor [22]. However, TAM also has some adverse events, including endometrial cancer and thrombopoiesis, which are more common in elderly postmenopausal women. Therefore, it is necessary to evaluate the treatment efficacy and side effects of the two kinds of drugs, AIs and TAM.

It has been proved that the third generation AIs have more advantages over TAM for postmenopausal IBC women with positive hormone receptor. Two large randomized, double blind trials [13, 14] in our meta-analysis compared the advantages and disadvantages for postmenopausal DCIS women with positive hormone receptor. Our study showed that ANA decreased the incidence of CBCR-INV compared with TAM, which was shown like the ATAC trial [23]. Side-effects were different between ANA and TAM. More events of thrombosis (including deep vein thrombosis and pulmonary thrombus), symptom of vasomotor or gynecological occurred in "TAM" group, while headache, osteoarticular disease and hypercholesteremia occurred in "ANA" group. It has been proved that menopausal hormone therapy increased the risk of ovarian cancer [24]. The IBIS-II DCIS trial [14] showed that TAM probably have greater potential to cause ovarian cancer than ANA. Therefore, for postmenopausal DCIS women with ER/PR positive, the selection of TAM or ANA was based on clinical characteristics and underlying disease of patients, as well as the side-effects of drugs.

Some limitations should be considered in this meta-analysis. First, the study lacked the data of patients' characteristics, such as age, tumor size, pathology and immunohistochemistry status. Second, the number of studies included was too small despite of large cases of each study, and then publication bias was not done. Third, there was a certain publication bias because of non-significant or negative findings which may not be published.

Conclusions

It was concluded that DCIS patients with positive hormone receptors should be recommended to receive endocrine therapy. Selection of TAM or ANA is based on clinical characteristics and underlying disease of patients, as well as the side-effects of drugs.

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Compliance with Ethical Standards

Conflict of Interest The author reports no conflicts of interest in this work.

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