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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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Abstract:

PURPOSE: Patients with metabolic syndrome have a higher risk of cardiovascular disease, although their susceptibility to chemotherapy-induced cardiac disease is not well documented. The aim of this meta-analysis was to assess the associations between overweight or obesity and cardiotoxicity from anthracycline and/or trastuzumab (TRZ) in breast cancer patients using a meta-analysis methodology.

METHODS: We performed a random-effects and a network meta-analysis and assessed publication bias. We included 15 studies and 8745 patients with localized and metastatic breast cancer treated with adjuvant or neo-adjuvant anthracyclines and/or TRZ.

RESULTS: The combination of overweight and obesity was significantly associated with a greater risk of developing cardiotoxicity after an anthracycline and/or trastuzumab regimen in breast cancer patients. The pooled odds ratio for cardiotoxicity was 1.38 (95% confidence interval (CI): 1.06, 1.80; I^2 = 43%; n =8745) for overweight or obesity (BMI>25), 1.47 (95% CI: 0.95, 2.28; I^2 =47%; n = 2615) for obesity and 1.15 (95% CI: 0.83, 1.58; I^2 =27%; n = 2708) for overweight. Associations were independent of the study design, year of publication, drug regimen (anthracyclines alone vs trastuzumab +/- anthracyclines) or definition of cardiotoxicity and of overweight/obesity. There was no evidence of publication bias.

CONCLUSION: Our findings consistently showed that overweight and obesity are risk factors for cardiotoxicity from both anthracyclines and trastuzumab in breast cancer patients.

Introduction

Anthracyclines are anticancer agents with a broad spectrum of activity in oncological practice [1]. However, the use of anthracyclines is limited by the acute and chronic dose-dependent cardiotoxicity they may induce [2-4]. Following the administration of anthracyclines in adjuvant setting of breast cancer, trastuzumab (TRZ, Herceptin®), a humanized monoclonal antibody against the human epidermal growth factor receptor 2 (HER 2 or ErbB2) protein[5], is effective in patients that overexpress this receptor. The combination of TRZ and chemotherapy provides a clinical benefit in terms of recurrence-free survival and overall survival compared with chemotherapy alone [6-9]. Nonetheless, while preclinical studies did not reveal cardiotoxicity [10], later clinical studies showed that treatment with TRZ led to an unexpected incidence of cardiac side effects [11,12]. The most frequent effect was reduced systolic ventricular function, asymptomatic or associated with heart failure [13].

Overweight and obesity are complex health problems that affect a growing number of populations, and which increases the risk of several chronic diseases including cancer [14]. Although it is has been known for years that patients with metabolic syndrome have a higher risk of cardiovascular disease [15], their susceptibility to chemotherapy-induced cardiac disease is not well documented. Moreover, obesity has recently been associated with poor outcomes (overall survival and disease-free survival) in breast cancer patients treated with DOX-based chemotherapy [16]. Conversely, other studies have indicated that BMI had no effect on disease-free survival, but only a significant negative impact on overall survival [17], suggesting that obese women with breast cancer have poorer overall survival, probably due to a higher risk of non-cancer-related causes of death, and also to an unfavorable socio-economic status and genetic background [19]. Therefore, it is important to explore in

greater depth the influence of overweight and obesity as aggravating factors in the development of cardiotoxicity, particularly in the context of anthracycline and/or trastuzumab-based therapy for breast cancer.

Methods

Search Strategy

We conducted comprehensive literature searches in PubMed, , Embase, Web of Science, Scopus, and clinicaltrials.gov using predefined keywords [(“anthracyclines” or “doxorubicin” or “epirubicin” or “trastuzumab”) and (“cardiac toxicity” or “cardiotoxicity” or “heart failure”) and (“BMI” or “body mass index” or “overweight” or “underweight” or “obesity” or “body weight”) and (“breast” or “breast cancer”)]. We used both Medical Subject Headings and text words in PubMed, and we used Emtree terms and text words in Embase. We used text words in Web of Science, Scopus, and clinicaltrials.gov. We included all languages, even though we did not identify any eligible non-English papers. We excluded case reports, reviews, guidelines, editorials, and letters. We checked the reference lists of included articles for additional studies. Moreover, we looked at the full text of studies on the associations of risk factors, and cardiotoxicity of either anthracyclines or trastuzumab to identify additional studies.

Selection of the Studies

The first author (C.G.) assessed the titles, abstracts, and full texts of the studies found and determined whether the studies examined the associations of weight-related factors with cardiotoxicity of anthracyclines and/or trastuzumab. We included cross-sectional and cohort studies as well as both population-based and hospital-based case-control studies in the systematic review. To be eligible for a meta-analysis, the studies had to report quantitative data on the association between overweight/obesity and cardiotoxicity of anthracyclines and/or trastuzumab. We also

contacted authors of studies that were potentially eligible for inclusion in the meta-analysis in order to obtain additional information or new results [20-22].

Quality Assessment

Two reviewers (C.G. and A.L.) independently assessed the quality of the study, using the Newcastle-Ottawa Scale adapted to the specific design of the study [23]. Disagreements between the two reviewers were resolved by consensus. The definition used for cardiotoxicity was also evaluated as adequate or not according to the classical definition and to the recent expert consensus on Cancer Therapeutics–Related Cardiac Dysfunction [24].

Meta-analysis

Firstly, the proportion of cardiotoxicity was estimated in a meta-analysis by pooling the proportion of patients with cardiotoxicity in individual studies, calculated as the proportion of patients with cardiotoxicity divided by the number of patients treated with anthracyclines and/or trastuzumab. An arcsine transformation was used to stabilize the variation of proportions [25]. A random effect model was used according to DerSimonian-Laird's method [26,27].

Secondly, paired and network meta-analyses were conducted to pool the effect sizes of the weight status (normal, overweight, or obese)on cardiotoxicity of anthracyclines and/or trastuzumab in patients treated for breast cancer. The use of meta-analyses as adjustment method avoids a bias called Simpson's paradox that can be encountered in simple addition of cases and population of each individual studies [28]. Network meta-analyses combine the information from direct evidence (pairwise comparisons) and indirect evidence (comparing B to C from the comparisons of A to

B and A to C). Odds ratio (OR), expressed with 95% confidence intervals (CI), were calculated. A random-effect model with the DerSimonian and Laird method was used. The estimate from a random-effects meta-analysis is more conservative than that from a fixed-effect meta-analysis [29]. Paired meta-analyses were performed using Stata 10 (metan add-on) [30]. Network meta-analyses were performed using R 3.1.0 software (package netmeta) according to the method described by Rücker [31,32]. This is a frequentist method based on electrical networks and graph theory that performs as well as the classical bayesian network analysis, without the need to specify priors and that is easier to implement [33]. Inconsistency was evaluated with Cochran's Q [34].

We assessed the presence of heterogeneity across the studies by means of the I^2 statistic [35]. The I^2 statistic shows the total variation across studies that is not due to chance. An I^2 statistic less than 25% indicates a small amount of inconsistency, and more than 50% indicates a large amount of inconsistency [36]. We used meta-regression to determine whether study-level covariates accounted for the observed heterogeneity. The main analyses were performed to compare the impact of overweight and obesity with that of normal weight. Subgroup analyses were conducted according to the treatment (anthracyclines only versus trastuzumab+/-anthracyclines). There was no data on trastuzumab cardiotoxicity alone (i.e. with a 0% rate of anthracyclines use in the population) in the included studies. We also performed subgroup analyses according to World Health Organization recommended cut-off points for body mass index (BMI; weight (kg)/height $(m)^2$) and defined overweight as BMI 25–29.9 and obesity as BMI ≥30 [37].

To assess publication bias, we used a funnel plot, which compared the sizes of the overweight/obesity effects with their standard errors. We used the Egger regression

test to examine funnel plot asymmetry. Statistical significance for publication bias was based on a P value less than 0.10 [38]

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) was used as guidance for reporting this meta-analysis [39].

Results

The review flow is depicted in Figure 1. Our searches initially identified 585 abstracts. There were 123 relevant studies on the associations of cardiac risk factors with cardiotoxicity of anthracyclines and/or trastuzumab in breast cancer patients. Obesity was evaluated as a potential risk factor of cardiotoxicity in 15 studies. Three of them were not included in the meta-analysis because the study population also included patients with non-breast malignancies. We contacted the authors of 14 other studies that were eligible for the assessment of cardiotoxicity but that did not mention obesity. Three of them were able to provide additional data about the proportion of obese patients in the cardiotoxicity and non- cardiotoxicity groups of their studies. Overall, 15 studies were included in the meta-analysis [4,12,20-22,40-49] (table 1 and 2): seven were prospective cohort studies and eight were retrospective cohort studies. Most of these studies only included patients with localized breast cancer (LBC) (9/15) with adjuvant and neo-adjuvant chemotherapies. Of the 15 studies included in this meta-analysis, four focused on anthracyclines cardiotoxicity, and 11 focused on trastuzumab +/- anthracyclines cardiotoxicity (the rates of anthracyclines use in the trastuzumab studies are described in the table 2). Of the 15 studies included in the review, 11 studies reported results for overweight, 15 reported results for overweight/obesity, and 11 reported results for obesity. Similar results were reported from cross-sectional, case-control, and cohort studies. Therefore, we combined all designs in a single analysis.

Overall study quality was satisfactory, although most studies stemmed from institutional databases and were retrospective (table 3).

Cardiotoxicity incidence

The mean rate of cardiotoxicity of the 8,745 patients analysed was 17% (95%CI: 11-25). Patients treated with anthracyclines only (n=3,898) had a rate of cardiotoxicity of 20% (95%CI: 5-43); whereas patients treated with trastuzumab +/- anthracyclines (n=4,847) had 16% (95%CI: 10-24) of cardiotoxicity.

Using a meta-analysis on the 11 studies including patients treated with TRZ, we found that 91 % (95%CI: 83-97) of the included patients were also treated with anthracyclines.

Overweight/obesity and cardiotoxicity

As shown in figure 2, the combination of overweight and obesity was significantly associated with a greater risk of developing cardiotoxicity after an anthracycline and/or trastuzumab regimen in breast cancer patients.

The pooled odds ratio for cardiotoxicity was 1.38 (95% confidence interval (CI): 1.06, 1.80; I^2 = 43%; n =8745) for overweight or obesity (BMI>25), 1.47 (95% CI: 0.95, 2.28; I^2 =47%; n = 2615) for obesity and 1.15 (95% CI: 0.83, 1.58; I^2 =27%; n = 2708) for overweight.

Moreover, there was no significant effect of the drug regimen on the role of overweight and obesity in the ~~onset~~ risk of cardiotoxicity (figure 3).

Using network meta-analysis ~~(figure 4)~~, the subgroup analysis showed a gradual increase in the risk with higher BMI (p=0.05): normal weight patients had the lowest risk of developing cardiotoxicity, overweight patients had an intermediate risk (OR= 1.13 [0.80; 1.61] vs normal weight)) and obese patients had the highest risk (OR= 1.27 [0.88; 1.86] vs overweight and OR=1.44 [0.99; 2.10] vs normal weight).

Heterogeneity and meta-regression

In this meta-analysis, the estimates of studies on the association between obesity or overweight and cardiotoxicity were moderately heterogeneous (I2 = 43%; figure 2).

In the meta-regression of the 15 studies on the association between overweight/obesity and cardiotoxicity, the heterogeneity across studies was not explained by study design, year of publication, geographic origin, drug regimen (anthracyclines alone vs trastuzumab +/- anthracyclines) or the definition of cardiotoxicity and of overweight/obesity. The proportion of anthracycline use in the studies was not associated with changes in the effect of overweight and obesity on cardiotoxicity by meta-regression analysis (β=2.09; p=0.22).

Publication bias

The funnel plot of data from the 15 studies included in the meta-analysis was symmetrical (Figure 4). The P value for the Egger test was 0.43.

Discussion

This network meta-analysis based on 15 studies and on 8,745 patients shows that overweight and obesity are significantly associated with the risk of cardiotoxicity from anthracycline and/or trastuzumab. In addition drug regimen (ie anthracyclines alone, or trastuzumab +/- anthracyclines) is not associated with a different effect of weight parameters on the cardiotoxicity risk.

Cardiotoxicity definition

Most of the included studies employed cardiotoxicity definitions that were considered adequate regarding to the consensual definition[50] used prior to the new expert consensus [24]. Moreover, in the meta-regression of the 15 studies on the association between overweight/obesity and cardiotoxicity, the heterogeneity across studies was not explained by the definition of cardiotoxicity. Thus, we can consider that the results were not significantly influenced by the slightly different definitions employed.

Rates of cardiotoxic events

In a recent meta-analysis on anthracyclines cardiotoxicity, clinically overt cardiotoxicity occurred in 6% (95%CI 3-9), whereas subclinical cardiotoxicity developed in 18% (95%CI 12-24)[51]. These rates are consistent with ours in anthracyclines patients (20% (95%CI 5-43)) and can be explained by the high rates of asymptomatic LVEF alterations. Concerning trastuzumab cardiotoxicity rates, Chen *et al* described in a meta-analysis on 11,882 patients from 10 randomized clinical trials (RCTs) that incidences of LVEF decrease and congestive heart failure (CHF) were 7.5% (95% CI 4.2–13.1) and 1.9% (95% CI 1.0–3.8) among patients receiving trastuzumab.[52] The incidence of LVEF decrease with trastuzumab for

anthracyclines-based chemotherapy was 7.2% (95%CI: 3.8–13.3), while it was 5.2% (95%CI: 0.2–56.6) for non-anthracycline containing chemotherapy. These rates are lower than those found in our study (trastuzumab + anthracyclines: 16% (95%CI 10-24)), probably because we mainly included observational studies derived from local cohorts of patients, although Chen *et al* only included RCTs, where the patients are carefully selected at admission and closely monitored. In a retrospective cohort analysis, Bowles *et al* demonstrated the cumulative heart failure/cardiomyopathy incidence among recipients of anthracycline and trastuzumab was 6.2% (95%CI 4.1-8.2) after 1 year of follow-up and continued to increase to 20.1% (95%CI 14-25.6) by 5 years[53]. Thus, the duration of follow-up could also explain the discrepancies of cardiotoxicity rates between our study and the literature data.

Regarding the rates of cardiotoxicity according to the drug regimen, we did not found a potentiation of anthracyclines cardiotoxicity when trastuzumab was also used. These results are discordant with those recently published by Thavendiranathan *et al* [54] who demonstrated in a large population-based retrospective cohort study that, compared to other drug regimens, breast cancer patients receiving a sequential therapy (anthracyclines followed by trastuzumab) had the highest risk of clinical cardiotoxicity as assessed by congestive heart failure or cardiac death. We suggest that the discrepancy between our results and Thavendiranathan *et al* could be due to a selection bias, since only the patients not developing a cardiotoxicity with anthracyclines are usually treated with TRZ. However, our study and our search strategy were not designed to evaluate specifically the rates of cardiotoxicity according to the different drug regimens, as suggested by the relatively large confidence intervals reported in the subgroup analysis. Thus potentials lack of power

in the population size and selection bias in the study selection could have reduced accuracy of our cardiotoxicity rates.

Obesity and cardiotoxicity

There is a well-established link between obesity and heart failure (HF) in the general population; Kenchaiah et al. reported the first large epidemiological study showing obesity to be an independent risk factor for development of HF, analyzing 5,881 individuals from the Framingham Heart Study. It was concluded that for each increment of 1 kg/m^2 in BMI, there was an increase in the risk of HF of 7 % for women and 5 % for men[55]. The risk of development of HF was independent of age, alcohol, and cigarette use and comorbidities including diabetes, hypertension, and history of myocardial infarction[56].The present work is the first to assess the potential role of overweight and obesity on the cardiac dysfunction induced both by anthracyclines and trastuzumab. The large population size allowed proper assessment of the excess risk associated with weight-related abnormalities. Obesity was associated with a poor outcome in breast cancer patients treated with anthracyclines-based chemotherapy [17], affecting both overall survival and disease-free survival, and remained an important prognostic factor, independent of the treatment dose [16,57]. This could be partly explained by the higher rates of cardiac adverse events encountered by obese patients treated with anthracyclines or trastuzumab. In fact, few studies have shown that obese patients [58] or rats fed with a high-lipid diet [59] are more sensitive to the cardiotoxic effects of anthracyclines. In an *in vivo* model of overweight induced by post-natal programming, we recently demonstrated that moderately overweight adult mice were more sensitive to cardiac systolic impairment and confirmed the potentiating action of TRZ on DOX-induced cardiotoxicity in lean mice [60]. The mechanisms by which overweight/obesity is able

to promote anthracyclines-induced cardiotoxicity may involve adiponectin down-regulation [61,62]. The dysregulation of adipocyte-derived hormones, adipocytokines, promotes the development of diverse obesity-linked diseases [63]. Plasma adiponectin levels are decreased in obese subjects [64]. ~~Adiponectin confers resistance to anthracyclines-induced myocardial damage through activation of Akt signalling within cardiomyocytes [62].~~ Adiponectin-KO mice showed exacerbated left ventricle contractile dysfunction following doxorubicin injection, whereas exogenous adiponectin improved doxorubicin-induced left ventricular dysfunction in wild-type and adiponectin-KO mice [62]. ~~It has also been demonstrated that metformin protects cardiomyocytes from doxorubicin-induced damage and that the cardiac adiponectin system plays an important role in this protective action [65].~~ However, no study has yet been performed to elucidate the role of adiponectin on trastuzumab-induced cardiac dysfunction.

~~Another explanation to the excess risk of cardiotoxicity carried by obese patients could be related to a different genetic background. Gene-expression profiles have revealed perturbed pathways involved in crosstalk between tumours and cardiac function [66]. In fact, the ATP Binding Cassette, subfamily B, member 1 gene (ABCB-1) genotype has been associated with a genetic risk of obesity, but also with various responses to chemotherapy in cancer patients. Moreover, another ABC family member, ABCB-8, which regulates the iron export inside the mitochondria, has recently been described as a target of DOX, leading to iron accumulation within this organelle, and thus to oxidative damages [67].~~

Limitations:

The present study has several limitations. Mainly, it was not possible to take into account the associated cardiac risk factors or the other classical anthracyclines and trastuzumab cardiotoxicity risk factors. Meta-regressions controlling other risk factors would have required obtaining individual data for each study that we did not obtain. Adjusted odds ratios were available in very few studies and could neither be used. However, adjusted odds ratios were similar to crude odds ratio when they were available [21,41,45]. Thus, the higher risk of cardiotoxicity for obese patients treated with these drugs could also be related to a higher prevalence of other risk factors in these patients. This could explain the moderate heterogeneity observed among the studies included in the analysis both regarding the rates of cardiotoxicity and the effect of overweight and obesity on ~~the onset of~~ cardiotoxicity. Most of the studies included were not designed to address specifically the matter of obesity as risk factor of drug-induced cardiotoxicity, leading to possible bias in data collection. Moreover, the definitions of both “obesity” and “overweight” as well as “cardiotoxicity” slightly differed among the studies involved. Finally, the subgroup analysis was limited by the relative lack of power related to the small number of studies that included all the three groups being compared. In addition, many studies included here reported limited details, and for several others, we combined the occurrence of clinical and subclinical cardiotoxicity as a single end point to increase statistical power.

Conclusion

Overweight and obesity are significantly associated with the risk of cardiotoxicity from anthracycline and/or trastuzumab. A careful assessment of cardiovascular risk factor is crucial to improve the risk stratification of cardiotoxicity in breast cancer patients treated with anthracyclines and trastuzumab. Further studies are needed to establish the independent predictive value of obesity on cardiotoxicity, but also to identify potential therapeutic targets to mitigate the increased cardiotoxicity risk associated with overweight and obesity.

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Tables and figures:

TABLE 1. Main features of included studies

TABLE 2. Internal validity of included studies according to the Newcastle-Ottawa scale

FIGURE 1. Review profile.

FIGURE 2. Results of a meta-analysis of the association between overweight or obesity and cardiotoxicity of anthracycline and/or trastuzumab in breast cancer patients. The size of the gray shaded area indicates the weight of each study. Horizontal lines show the 95% confidence intervals (CIs). OR, odds ratio. MH: Mantel-Haenzsel method. DL: DerSimonian and Leard method.

FIGURE 3. Results of a meta-analysis of the association between overweight and obesity and ~~the onset of~~ cardiotoxicty in breast cancer patients treated with anthracycline and/or trastuzumab. The size of the gray shaded area indicates the weight of each study. Horizontal lines show the 95% confidence intervals (CIs). OR, odds ratio. MH : Mantel-Haenzsel method. DL : DerSimonian and Leard method.

~~**Figure 4.** ***ONLINE ONLY*** Results of network meta-analysis of the association of overweight or obesity with cardiotoxicity of anthracycline and/or trastuzumab in breast cancer patients. OR, odds ratio.~~

FIGURE 4. ***ONLINE ONLY*** Publication bias in studies on the associations of overweight/obesity (15 studies) with cardiotoxicity of anthracyclines and/or trastuzumab.

Table 1. Main features of included studies

First Author	Patients	Year	Location	Breast cancer	Setting	Overweight definition	Obesity definition	Cardiotoxicity rates	Anthracyclines treatment rates	TRZ	Cardiotoxicity definition
Aitelhaj[40]	100	2013	Morocco	LBC HER2+	Adjuvant + neo-adjuvant	BMI>25	BMI≥30	38%	100%	yes	LVEF decrease below 50% or an absolute decrease of >10 points below the baseline value or any symptoms or CHF
Ayres[41]	79	2015	Brazil	LBC HER2+	Adjuvant +neo-adjuvant	BMI>25	BMI>30	33%	91%	yes	CHF or a decrease in LVEF by ≥10 % compared to the first echocardiography measurement or <50% at any time
Bonneterre[42]	67	2004	France	LBC	Adjuvant	BMI>27	NA	31%	100%	no	LVEF <50%, a decrease in LVEF >20% of baseline value, or CHF
Caram[4]	165	2015	USA	LBC	Adjuvant +neo-adjuvant	BMI≥25	BMI≥30	12%	100%	yes	Systolic dysfunction = LVEF<55 %
Cardinale[21]	251	2010	Italy	LBC + MBC HER2+	Adjuvant +neo-adjuvant	BMI>25	BMI≥30	17%	78%	yes	An absolute drop ≥10% from baseline and <50%
Cardinale[20]	669	2015	Italy	LBC + MBC	Adjuvant +neo-adjuvant	BMI>25	BMI≥30	10%	100%	no	An absolute drop ≥10% from baseline and <50%
Farolfi[12]	179	2013	Italy	LBC	Adjuvant	BMI≥25	BMI≥30	44%	91%	yes	an absolute LVEF decrease ≥15 points from baseline or a LVEF<50%
Fumoleau[44]	3073	2007	France	LBC	Adjuvant	BMI≥27	NA	1%	100%	no	The occurrence of cardiac symptoms, a LVEF below normal value of the center, and/or a LVEF decrease <20% of baseline value
Gomes[43]	237	2014	Brazil	LBC HER2+	Adjuvant +neo-adjuvant	BMI>25	NA	20%	84%	yes	Cardiac death or absolute decrease in LVEF > 10% to a value less than 50%, or CHF
Lemieux[45]	237	2013	Canada	LBC HER2+	Adjuvant +neo-adjuvant	BMI≥25	BMI≥30	14%	73%	yes	A decrease >10% from baseline with a resulting LVEF <45%
Perez[46]	1280	2008	Wordlwide	LBC HER2+	Adjuvant	BMI≥25	BMI≥30	3%	100%	yes	LVEF decreased >15 percentage points, or 10 to 15 percentage points to below the LLN, relative to registration LVEF level
Serrano[47]	89	2013	Spain	NA	NA	BMI>25	BMI>30	57%	100%	no	CHF, sudden cardiac death, left ventricular systolic or diastolic dysfunction appeared during the follow-up
Suter[48]	1667	2007	Wordlwide	LBC HER2+	Adjuvant +neo-adjuvant	BMI>25	NA	4%	94%	yes	Absolute drop of LVEF ≥10% with a final LVEF <50% or cardiac death or severe CHF

Urun[49]	52	2015	Turkey	LBC HER2+	Adjuvant +neo-adjuvant	BMI>25	BMI>30	10%	75%	yes	CHF or >10% decline of LVEF
Yu[22]	608	2015	USA	LBC HER2+	Adjuvant	BMI≥25	BMI≥30	11%	80%	yes	An absolute decline ≥16 % points from baseline LVEF or an absolute decline of 10–15 % points from baseline LVEF to below the LLN (55 %).

BMI indicates body mass index; LBC: localized breast cancer; MBC: metastatic breast cancer; NA: not available USA TRZ CHF indicates congestive heart failure; LVEF: left ventricular ejection fraction; LLN: lower limit of normal.

Table 2. Internal validity of included studies according to the Newcastle-Ottawa scale *

First Author	Study Design	Data Source	Demonstration that outcome was not present at start	Adequacy of follow-up	Adequacy of cardiotoxicity definition
Aitelhaj[40]	Retrospective	Institutional database	yes	probably yes	yes
Ayres[41]	Retrospective	Institutional database	no	probably yes	yes
Bonneterre[42]	Prospective	Post hoc analysis of RCT	yes	yes	yes
Caram[4]	Retrospective	Institutional database	no	probably yes	no
Cardinale[21]	Prospective	Institutional database	yes	yes	yes
Cardinale[20]	Prospective	Institutional database	yes	yes	yes
Farolfi[12]	Retrospective	Institutional database	no	probably yes	yes
Fumoleau[44]	Retrospective	Post hoc analysis of RCT	yes	yes	yes
Gomes[43]	Retrospective	Institutional database	no	no	yes
Lemieux[45]	Retrospective	Institutional database	no	yes	yes
Perez[46]	Prospective	Post hoc analysis of RCT	yes	yes	yes
Serrano[47]	Prospective	Institutional database	yes	no	no
Suter[48]	Prospective	Post hoc analysis of RCT	yes	yes	yes
Urun[49]	Prospective	Institutional database	yes	no	yes
Yu[22]	Retrospective	Institutional database	no	no	yes

- All other items of the Newcastle-Ottawa Scale were scored as adequate/low risk of bias. RCT : randomized clinical trial

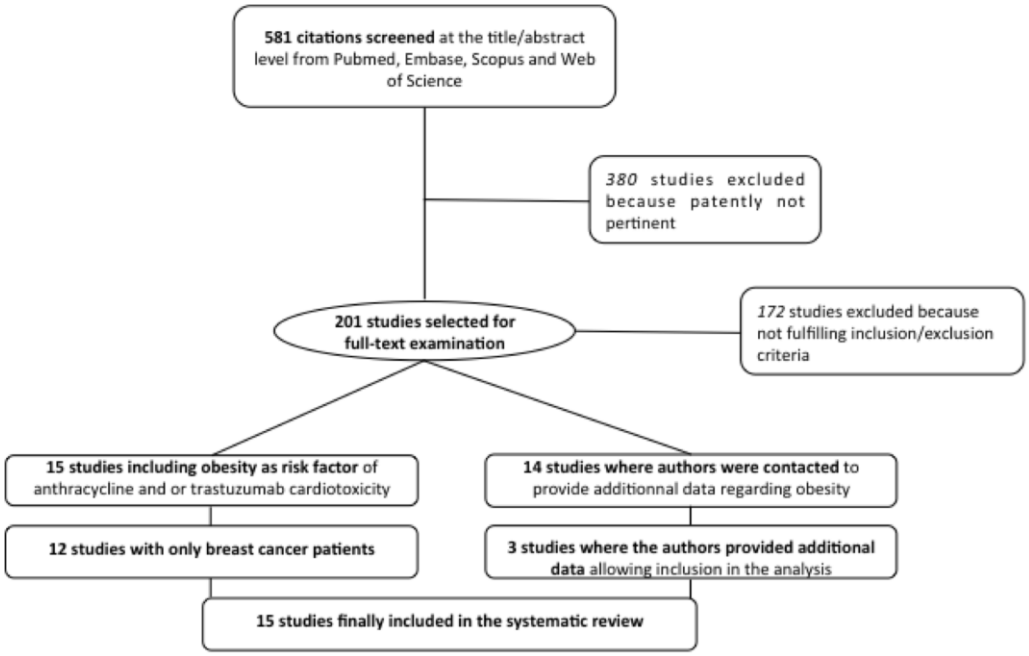

FIGURE 1

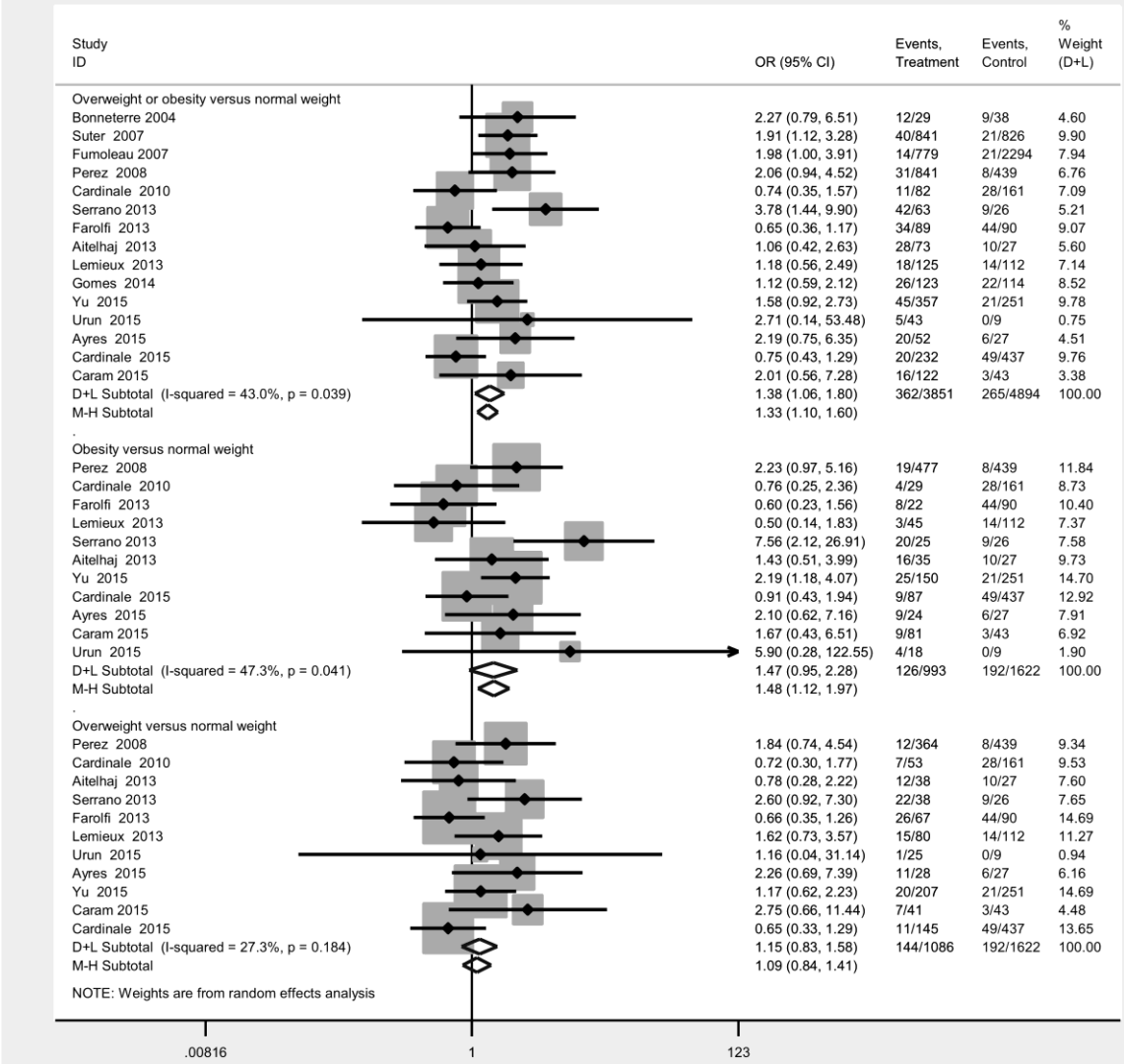
Study ID
OR (95% CI)
Events, Treatment
Events, Control
% Weight (D+L)
Overweight or obesity versus normal weight
Bonneterre 2004 2.27 (0.79, 6.51) 12/29 9/38 4.60
Suter 2007 1.91 (1.12, 3.28) 40/841 21/826 9.90
Fumoleau 2007 1.98 (1.00, 3.91) 14/779 21/2294 7.94
Perez 2008 2.06 (0.94, 4.52) 31/841 8/439 6.76
Cardinale 2010 0.74 (0.35, 1.57) 11/82 28/161 7.09
Serrano 2013 3.78 (1.44, 9.90) 42/63 9/26 5.21
Farolfi 2013 0.65 (0.36, 1.17) 34/89 44/90 9.07
Aitelhaj 2013 1.06 (0.42, 2.63) 28/73 10/27 5.60
Lemieux 2013 1.18 (0.56, 2.49) 18/125 14/112 7.14
Gomes 2014 1.12 (0.59, 2.12) 26/123 22/114 8.52
Yu 2015 1.58 (0.92, 2.73) 45/357 21/251 9.78
Urun 2015 2.71 (0.14, 53.48) 5/43 0/9 0.75
Ayres 2015 2.19 (0.75, 6.35) 20/52 6/27 4.51
Cardinale 2015 0.75 (0.43, 1.29) 20/232 49/437 9.76
Caram 2015 2.01 (0.56, 7.28) 16/122 3/43 3.38
D+L Subtotal (I-squared = 43.0%, p = 0.039) 1.38 (1.06, 1.80) 362/3851 265/4894 100.00
M-H Subtotal 1.33 (1.10, 1.60)
Obesity versus normal weight
Perez 2008 2.23 (0.97, 5.16) 19/477 8/439 11.84
Cardinale 2010 0.76 (0.25, 2.36) 4/29 28/161 8.73
Farolfi 2013 0.60 (0.23, 1.56) 8/22 44/90 10.40
Lemieux 2013 0.50 (0.14, 1.83) 3/45 14/112 7.37
Serrano 2013 7.56 (2.12, 26.91) 20/25 9/26 7.58
Aitelhaj 2013 1.43 (0.51, 3.99) 16/35 10/27 9.73
Yu 2015 2.19 (1.18, 4.07) 25/150 21/251 14.70
Cardinale 2015 0.91 (0.43, 1.94) 9/87 49/437 12.92
Ayres 2015 2.10 (0.62, 7.16) 9/24 6/27 7.91
Caram 2015 1.67 (0.43, 6.51) 9/81 3/43 6.92
Urun 2015 5.90 (0.28, 122.55) 4/18 0/9 1.90
D+L Subtotal (I-squared = 47.3%, p = 0.041) 1.47 (0.95, 2.28) 126/993 192/1622 100.00
M-H Subtotal 1.48 (1.12, 1.97)
Overweight versus normal weight
Perez 2008 1.84 (0.74, 4.54) 12/364 8/439 9.34
Cardinale 2010 0.72 (0.30, 1.77) 7/53 28/161 9.53
Aitelhaj 2013 0.78 (0.28, 2.22) 12/38 10/27 7.60
Serrano 2013 2.60 (0.92, 7.30) 22/38 9/26 7.65
Farolfi 2013 0.66 (0.35, 1.26) 26/67 44/90 14.69
Lemieux 2013 1.62 (0.73, 3.57) 15/80 14/112 11.27
Urun 2015 1.16 (0.04, 31.14) 1/25 0/9 0.94
Ayres 2015 2.26 (0.69, 7.39) 11/28 6/27 6.16
Yu 2015 1.17 (0.62, 2.23) 20/207 21/251 14.69
Caram 2015 2.75 (0.66, 11.44) 7/41 3/43 4.48
Cardinale 2015 0.65 (0.33, 1.29) 11/145 49/437 13.65
D+L Subtotal (I-squared = 27.3%, p = 0.184) 1.15 (0.83, 1.58) 144/1086 192/1622 100.00
M-H Subtotal 1.09 (0.84, 1.41)
NOTE: Weights are from random effects analysis
.00816
1
123

FIGURE 2

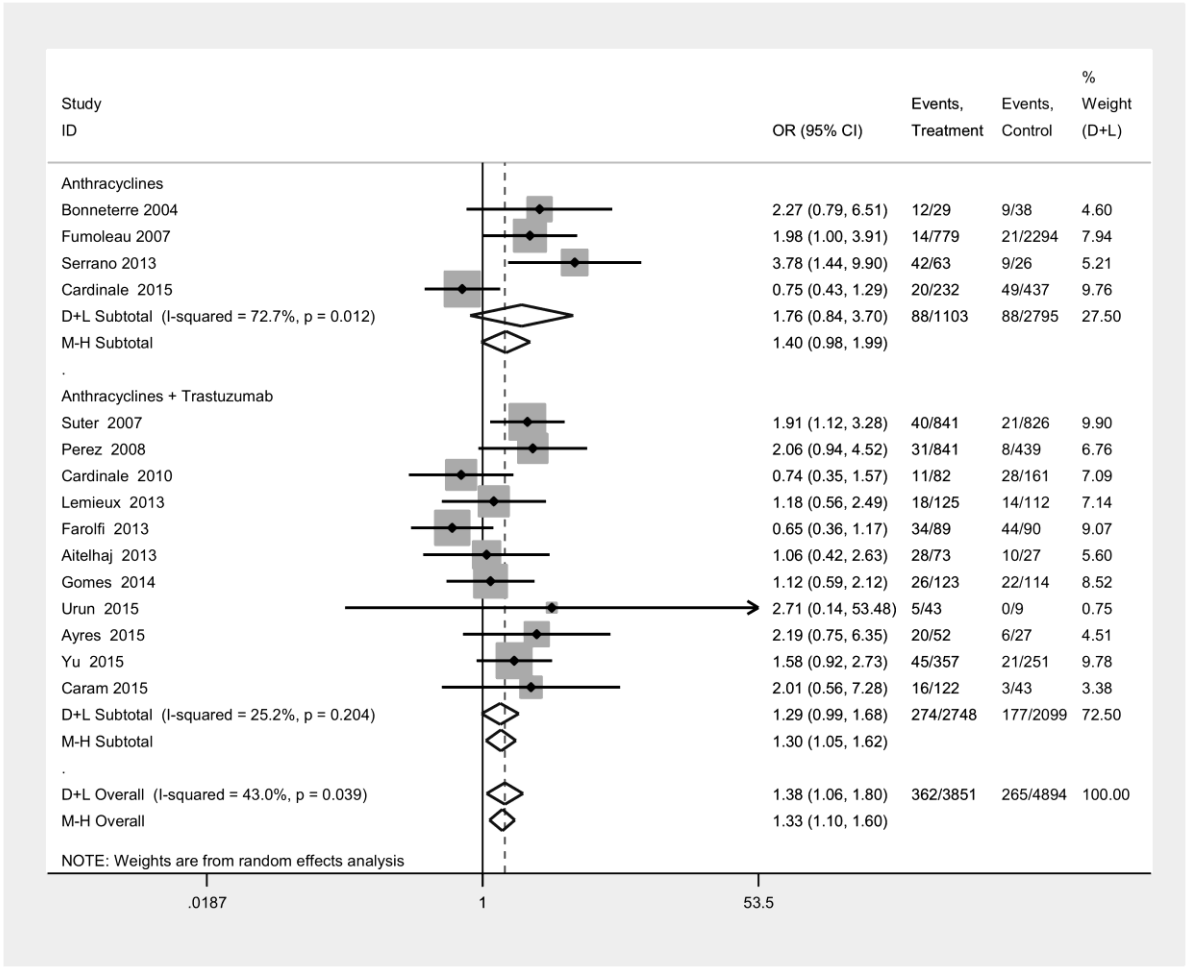
Study
ID
OR (95% CI)
Events, Treatment
Events, Control
% Weight (D+L)
Anthracyclines
Bonneterre 2004 2.27 (0.79, 6.51) 12/29 9/38 4.60
Fumoleau 2007 1.98 (1.00, 3.91) 14/779 21/2294 7.94
Serrano 2013 3.78 (1.44, 9.90) 42/63 9/26 5.21
Cardinale 2015 0.75 (0.43, 1.29) 20/232 49/437 9.76
D+L Subtotal (I-squared = 72.7%, p = 0.012) 1.76 (0.84, 3.70) 88/1103 88/2795 27.50
M-H Subtotal 1.40 (0.98, 1.99)
Anthracyclines + Trastuzumab
Suter 2007 1.91 (1.12, 3.28) 40/841 21/826 9.90
Perez 2008 2.06 (0.94, 4.52) 31/841 8/439 6.76
Cardinale 2010 0.74 (0.35, 1.57) 11/82 28/161 7.09
Lemieux 2013 1.18 (0.56, 2.49) 18/125 14/112 7.14
Farolfi 2013 0.65 (0.36, 1.17) 34/89 44/90 9.07
Aitelhaj 2013 1.06 (0.42, 2.63) 28/73 10/27 5.60
Gomes 2014 1.12 (0.59, 2.12) 26/123 22/114 8.52
Urun 2015 2.71 (0.14, 53.48) 5/43 0/9 0.75
Ayres 2015 2.19 (0.75, 6.35) 20/52 6/27 4.51
Yu 2015 1.58 (0.92, 2.73) 45/357 21/251 9.78
Caram 2015 2.01 (0.56, 7.28) 16/122 3/43 3.38
D+L Subtotal (I-squared = 25.2%, p = 0.204) 1.29 (0.99, 1.68) 274/2748 177/2099 72.50
M-H Subtotal 1.30 (1.05, 1.62)
D+L Overall (I-squared = 43.0%, p = 0.039) 1.38 (1.06, 1.80) 362/3851 265/4894 100.00
M-H Overall 1.33 (1.10, 1.60)
NOTE: Weights are from random effects analysis
.0187
1
53.5

FIGURE 3

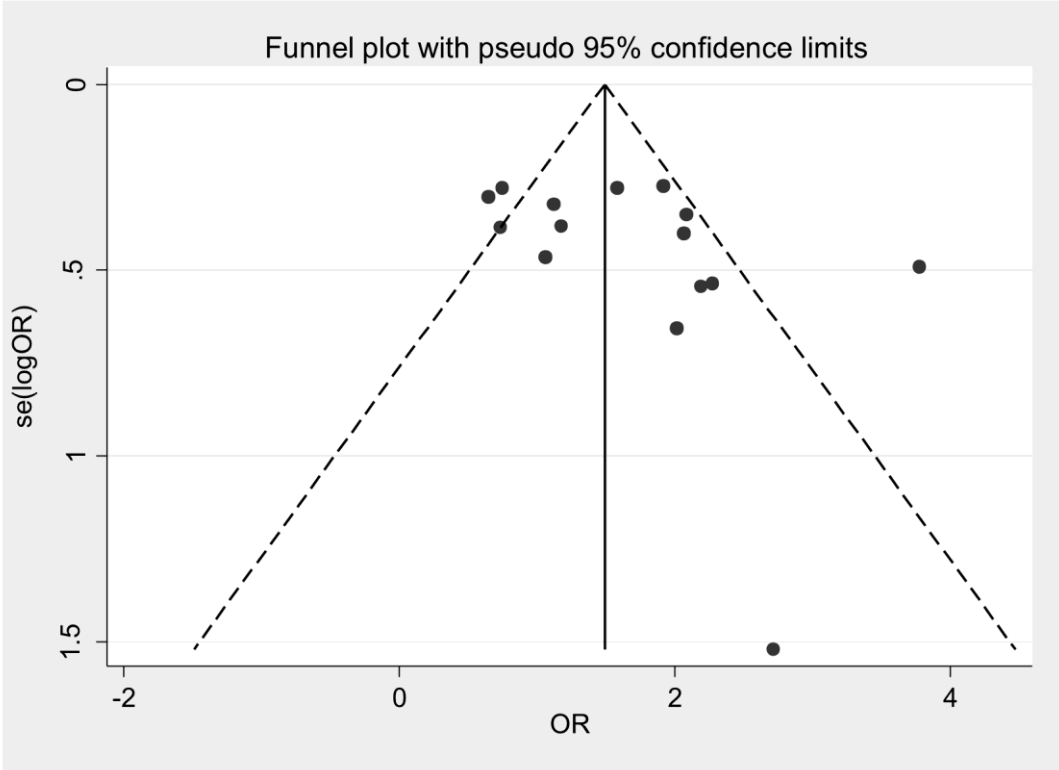

FIGURE 4 ONLINE ONLY