Obesity As a Risk Factor for Anthracyclines and Trastuzumab Cardiotoxicity in Breast Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

Purpose

Patients with metabolic syndrome have a greater 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 associations between obesity or being overweight and cardiotoxicity from anthracyclines and sequential anthracyclines and trastuzumab in patients with breast cancer.

Methods

We performed a random-effects analysis and a network meta-analysis and assessed publication bias. We included 15 studies and 8,745 patients with breast cancers who were treated with anthracyclines and sequential anthracyclines and trastuzumab.

Results

Combination of obesity and being overweight was significantly associated with a greater risk of developing cardiotoxicity after anthracyclines and a sequential anthracyclines and trastuzumab regimen in patients with breast cancer. Pooled odds ratio for cardiotoxicity was 1.38 (95% CI, 1.06 to 1.80; $I^2 = 43\%$; $N = 8,745$) for overweight or obesity (body mass index $> 25 \text{ kg/m}^2$), 1.47 (95% CI, 0.95 to 2.28; $I^2 = 47\%$; $n = 2,615$) for obesity, and 1.15 (95% CI, 0.83 to 1.58; $I^2 = 27\%$; $n = 2,708$) for overweight. Associations were independent of study design, year of publication, drug regimen (anthracyclines alone v sequential anthracyclines and trastuzumab), or definitions of cardiotoxicity and of overweight or obesity. There was no evidence of publication bias; however, we could not separate the contributions of obesity-related cardiovascular risk factors, such as diabetes and hypertension, from that of obesity itself in this largely unadjusted analysis.

Conclusion

Our findings in a largely unadjusted analysis suggest that overweight and obesity are risk factors for cardiotoxicity from anthracyclines and sequential anthracyclines and trastuzumab.

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INTRODUCTION

Anthracyclines are anticancer agents with a broad spectrum of activity in oncological practice¹; however, use of anthracyclines is limited by the acute and chronic dose-dependent cardiotoxicity they may induce.²⁻⁴ After administration of anthracyclines in an adjuvant setting of breast cancer, trastuzumab (Herceptin; Genentech, South San Francisco, CA), a humanized monoclonal antibody against the human epidermal growth factor receptor 2 (HER2 or ErbB2) protein,⁵ is effective in patients who overexpress this receptor. Combination of trastuzumab and

chemotherapy provides a clinical benefit in terms of disease-free survival and overall survival compared with chemotherapy alone.⁶⁻⁹ Nonetheless, whereas preclinical studies did not reveal cardiotoxicity,¹⁰ later clinical studies showed that treatment with trastuzumab led to an unexpected incidence of cardiac adverse effects,^{11,12} the most frequent of which was reduced left systolic ventricular function, which was asymptomatic or associated with heart failure.¹³

Being overweight and obesity are complex health problems that affect a growing number of populations and which increase the risk of several chronic diseases, including cancer.¹⁴ Although it 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 patients with breast cancer who were treated with doxorubicin-based chemotherapy.¹⁶ Conversely, other studies have indicated that body mass index (BMI) had no effect on disease-free survival, but only a significant negative impact on overall survival,¹⁷ which suggested that obese women with breast cancer have poorer overall survival, possibly as a result of a higher risk of noncancer-related causes of death, as well as an unfavorable socioeconomic status and genetic background.¹⁸ Therefore, it is important to explore in greater depth the influence of overweight and obesity as aggravating factors in the development of cardiotoxicity, in particular, in the context of anthracyclines and sequential anthracyclines and 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 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 meta-analysis, studies had to report quantitative data on the association between overweight and/or obesity and cardiotoxicity of anthracyclines and/or trastuzumab. We also contacted authors of studies that were potentially eligible for inclusion in the meta-analysis to obtain additional information or new results.^{19–21}

Quality Assessment

Two reviewers (C.G. and A.L.) independently assessed the quality of the study by using the Newcastle-Ottawa Scale adapted to the specific design of the study.²² Disagreements between the two reviewers were resolved by consensus. The definition used for cardiotoxicity was also evaluated as adequate or not according to the classic definition and to the recent expert consensus on Cancer Therapeutics–Related Cardiac Dysfunction.²³

Meta-Analysis

First, the proportion of cardiotoxicity was estimated in a meta-analysis by pooling the proportion of patients with cardiotoxicity in

individual studies, which was calculated as the proportion of patients with cardiotoxicity divided by the number of patients who were treated with anthracyclines and/or trastuzumab. An arcsine transformation was used to stabilize the variation of proportions.²⁴ A random-effect model was used according to DerSimonian-Laird's method.^{25,26}

Second, paired and network meta-analyses were conducted to pool the effect sizes of the weight status (normal weight, overweight, or obese) on the cardiotoxicity of anthracyclines and/or trastuzumab in patients who were treated for breast cancer. Use of meta-analyses as an adjustment method avoids a bias called Simpson's paradox, which can be encountered in simple additions of patients and populations of each individual study.²⁷ Network meta-analyses combine the information from direct evidence (pairwise comparisons) and indirect evidence (comparing B to C from comparisons of A to B and A to C). Odds ratios (OR), expressed with 95% CI, were calculated. A random-effect model with the DerSimonian-Laird method was used. The estimate from a random-effects meta-analysis is more conservative than that from a fixed-effect meta-analysis.²⁸ Paired meta-analyses were performed by using STATA 10 (metan add-on; STATA, College Station, TX; Computing Resource Center, Santa Monica, CA).²⁹ Network meta-analyses were performed by using R 3.1.0 software (netmeta package; The R Foundation, Vienna, Austria) according to the method described by Rücker.^{30,31} This is a frequentist method that is based on electrical networks and graph theory. It performs as well as the classic Bayesian network analysis, without the need to specify priors, and is easier to implement.³² Inconsistency was evaluated with Cochran's Q.³³

We assessed the presence of heterogeneity across the studies by means of the I^2 statistic.³⁴ The I^2 statistic shows the total variation across studies that is not a result of chance. An I^2 statistic < 25% indicates a small amount of inconsistency, and > 50% indicates a large amount of inconsistency.³⁵ We used meta-regression to determine whether study-level covariates accounted for the observed heterogeneity. 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 v trastuzumab with or without anthracyclines). The specific cardiotoxicity of trastuzumab alone was not assessable in the absence of individual data as all of the studies that included trastuzumab had a proportion of patients who were also treated with anthracyclines. We also performed subgroup analyses according to WHO recommended cutoff points for BMI [weight (kg)/height (m²)] and defined overweight as BMI 25 to 29.9 and obesity as BMI $\geq$ 30.³⁶

To assess publication bias, we used a funnel plot, which compared the sizes of the overweight or 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 < .10.³⁷

Preferred Reporting Items for Systematic reviews and Meta-Analyses was used as guidance for reporting this meta-analysis.³⁸

RESULTS

The review flow is depicted in Figure 1. Our searches initially identified 581 abstracts. There were 123 relevant studies on the associations of cardiac risk factors with anthracyclines and sequential anthracyclines and trastuzumab cardiotoxicity in patients with breast cancer. Obesity was evaluated as a potential risk factor of cardiotoxicity in 15 studies; three of these were not included in the meta-analysis because the study population also included patients with nonbreast malignancies. We contacted the authors of 14 other studies that were eligible for the assessment of cardiotoxicity but did not mention obesity; three of them were able to provide additional data about the proportion of obese patients in the cardiotoxicity and noncardiotoxicity groups of their studies. Overall, we included 15 studies and 8,745 patients with localized and metastatic breast cancers who were treated with anthracyclines

Fig 1. Review profile.

and sequential anthracyclines and trastuzumab (Table 1): seven were prospective cohort studies and eight were retrospective cohort studies. Most of these studies only included patients with localized breast cancer (11 of 15 studies) with adjuvant and neo-adjuvant chemotherapies. Patients with metastatic breast cancer were treated with anthracyclines and trastuzumab in the metastatic setting and accounted for a relatively small proportion of the patients included. Of the 15 studies included in this meta-analysis, four focused on anthracycline cardiotoxicity and 11 focused on trastuzumab with or without anthracycline cardiotoxicity—rates of anthracycline use in the trastuzumab studies are described in Table 1. Of the 15 studies, 11 reported results for overweight, 15 reported results for overweight or 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 2).

Cardiotoxicity Incidence

Mean rate of cardiotoxicity of the 8,745 patients analyzed was 17% (95% CI, 11 to 25). Patients treated with anthracyclines only (n = 3,898) had a rate of cardiotoxicity of 20% (95% CI, 5 to 43), whereas patients treated with trastuzumab with or without anthracyclines (n = 4,847) had a 16% (95% CI, 10 to 24) rate of cardiotoxicity.

By using a meta-analysis of the 11 studies that included patients treated with trastuzumab, we found that 91% (95% CI, 83 to 97) of the included patients were also treated with anthracyclines.

Overweight or 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 anthracyclines and sequential anthracyclines and trastuzumab regimen in patients with breast cancer.

Pooled odds ratio for cardiotoxicity was 1.38 (95% CI, 1.06 to 1.80; $I^2 = 43\%$; N = 8,745) for overweight or obesity (BMI > 25), 1.47 (95% CI, 0.95 to 2.28; $I^2 = 47\%$; n = 2,615) for obesity, and 1.15 (95% CI, 0.83 to 1.58; $I^2 = 27\%$; n = 2,708) for overweight.

Moreover, there was no significant effect of the drug regimen on the impact of overweight and obesity on the risk of cardiotoxicity (Fig 3).

By using network meta-analysis, subgroup analysis showed a gradual increase in the risk with higher BMI ($P = .05$): normal-weight patients had the lowest risk of developing cardiotoxicity, overweight patients had an intermediate risk [OR, 1.13 (95% CI, 0.80; 1.61) ν normal-weight patients], and obese patients had the highest risk [OR, 1.27 (95% CI, 0.88; 1.86) ν overweight and OR, 1.44 (95% CI, 0.99; 2.10) ν normal-weight patients].

Heterogeneity and Metaregression

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

In the metaregression of the 15 studies on the association between overweight or obesity and cardiotoxicity, heterogeneity across studies was not explained by study design, year of publication, geographic origin, drug regimen (anthracyclines alone ν trastuzumab with or without anthracyclines), or the definition of cardiotoxicity and overweight or obesity. The proportion of

Table 1. Main Features of Included Studies

Study	No. of Patients	Year	Location	Type of Breast Cancer	Setting	Overweight Definition	Obesity Definition	Cardiotoxicity Rate, %	Anthracyclines Treatment Rate, %	Trastuzumab	Cardiotoxicity Definition
Altahaj et al ³⁹	100	2013	Morocco	LBC HER2-positive	Adjuvant + neo-adjuvant	BMI > 25	BMI ≥ 30	38	100	Yes	LVEF decrease below 50% or an absolute decrease of > 10 points below baseline value or any symptoms or CHF
Ayres et al ⁴⁰	79	2015	Brazil	LBC HER2-positive	Adjuvant + neo-adjuvant	BMI > 25	BMI > 30	33	91	Yes	CHF or a decrease in LVEF by ≥ 10% compared with first echocardiography measurement or < 50% at any time
Bonneterre et al ⁴¹	67	2004	France	LBC	Adjuvant	BMI > 27	NA	31	100	No	LVEF < 50%, a decrease in LVEF > 20% of baseline value, or CHF
Caram et al ⁴	165	2015	United States	LBC	Adjuvant + neo-adjuvant	BMI ≥ 25	BMI ≥ 30	12	100	Yes	Systolic dysfunction = LVEF < 55%
Cardinale et al ²⁰	251	2010	Italy	LBC + MBC HER2-positive	Adjuvant + neo-adjuvant	BMI > 25	BMI ≥ 30	17	78	Yes	An absolute drop ≥ 10% from baseline and < 50%
Cardinale et al ¹⁹	669	2015	Italy	LBC + MBC	Adjuvant + neo-adjuvant	BMI > 25	BMI ≥ 30	10	100	No	An absolute drop of ≥ 10% from baseline and < 50%
Da Fonseca et al ⁴³	237	2014	Brazil	LBC HER2-positive	Adjuvant + neo-adjuvant	BMI > 25	NA	20	84	Yes	Cardiac death or absolute decrease in LVEF of > 10% to < 50% or CHF
Farolfi et al ¹²	179	2013	Italy	LBC	Adjuvant	BMI ≥ 25	BMI ≥ 30	44	91	Yes	An absolute LVEF decrease of ≥ 15 points from baseline or an LVEF < 50%
Fumoleau et al ⁴²	3,073	2006	France	LBC	Adjuvant	BMI ≥ 27	NA	1	100	No	Occurrence of cardiac symptoms, an LVEF below normal value of the center, and/or an LVEF decrease of < 20% of baseline value
Lemieux et al ⁴⁴	237	2013	Canada	LBC HER2-positive	Adjuvant + neo-adjuvant	BMI ≥ 25	BMI ≥ 30	14	73	Yes	A decrease of > 10% from baseline, with a resulting LVEF of < 45%
Perez et al ⁴⁵	1,280	2008	Worldwide	LBC HER2-positive	Adjuvant	BMI ≥ 25	BMI ≥ 30	3	100	Yes	LVEF decreased > 15 percentage points, or 10-15 percentage points to below the LLN, relative to registration LVEF level
Serrano et al ⁴⁶	89	2013	Spain	LBC + MBC	NA	BMI > 25	BMI > 30	57	100	No	CHF, sudden cardiac death, left ventricular systolic or diastolic dysfunction appearing during follow-up
Suter et al ⁴⁷	1,667	2007	Worldwide	LBC HER2-positive	Adjuvant + neo-adjuvant	BMI > 25	NA	4	94	Yes	Absolute drop of LVEF of ≥ 10%, with a final LVEF < 50% or cardiac death or severe CHF
Ürün et al ⁴⁸	52	2015	Turkey	LBC + MBC HER2-positive	Adjuvant + neo-adjuvant	BMI > 25	BMI > 30	10	75	Yes	CHF or > 10% decline of LVEF
Yu et al ²¹	608	2015	United States	LBC HER2-positive	Adjuvant	BMI ≥ 25	BMI ≥ 30	11	80	Yes	An absolute decline of ≥ 16% points from baseline LVEF or an absolute decline of 10%-15% points from baseline LVEF to below the LLN (55%)

Abbreviations: BMI, body mass index; CHF, congestive heart failure; HER2, human epidermal growth factor receptor 2; LBC, localized breast cancer; LLN, lower limit of normal; LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer; NA, not available.

Table 2. Internal Validity of Included Studies According to the Newcastle-Ottawa Scale

Study	Study Design	Data Source	Demonstration That Outcome Was Not Present at Start	Adequacy of Follow-Up	Adequacy of Cardiotoxicity Definition
Aitelhaj et al ³⁹	Retrospective	Institutional database	Yes	Probably yes	Yes
Ayres et al ⁴⁰	Retrospective	Institutional database	No	Probably yes	Yes
Bonneterre et al ⁴¹	Prospective	Post hoc analysis of RCT	Yes	Yes	Yes
Caram et al ⁴	Retrospective	Institutional database	No	Probably yes	No
Cardinale et al ²⁰	Prospective	Institutional database	Yes	Yes	Yes
Cardinale et al ¹⁹	Prospective	Institutional database	Yes	Yes	Yes
Da Fonseca et al ⁴³	Retrospective	Institutional database	No	No	Yes
Farolfi et al ¹²	Retrospective	Institutional database	No	Probably yes	Yes
Fumoleau et al ⁴²	Retrospective	Post hoc analysis of RCT	Yes	Yes	Yes
Lemieux et al ⁴⁴	Retrospective	Institutional database	No	Yes	Yes
Perez et al ⁴⁵	Prospective	Post hoc analysis of RCT	Yes	Yes	Yes
Serrano et al ⁴⁶	Prospective	Institutional database	Yes	No	No
Suter et al ⁴⁷	Prospective	Post hoc analysis of RCT	Yes	Yes	Yes
Ürün et al ⁴⁸	Prospective	Institutional database	Yes	No	Yes
Yu et al ²¹	Retrospective	Institutional database	No	No	Yes

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

anthracycline use in the studies was not associated with changes in the effect of overweight and obesity on cardiotoxicity by meta-regression analysis ($\beta = 2.09$; $P = .22$).

Publication Bias

The funnel plot of data from the 15 studies included in the meta-analysis was symmetrical (Appendix Fig A1, online only). The P value for the Egger test was .43.

DISCUSSION

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

Cardiotoxicity Definition

Most of the included studies used cardiotoxicity definitions (Table 1) that were considered adequate according to the consensual definition⁴⁹ used before the new expert consensus.²³ Moreover, in the metaregression of the 15 studies on the association between overweight or obesity and cardiotoxicity, 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 used.

Rates of Cardiotoxic Events

In a recent meta-analysis on anthracycline cardiotoxicity, clinically overt cardiotoxicity occurred in 6% (95% CI, 3 to 9) of patients, whereas subclinical cardiotoxicity developed in 18% (95% CI, 12 to 24) of patients.⁵⁰ These rates are consistent with ours

in patients who received anthracycline [20% (95% CI, 5 to 43)] and can be explained by the high rates of asymptomatic left ventricular ejection fraction alterations. Concerning trastuzumab cardiotoxicity rates, the largest adjuvant clinical trials (Breast Cancer International Research Group,⁵¹ NSABP B-31⁸) reported rates of left ventricular ejection fraction decline from 14% to 20%.⁵² These are likely an underestimate given that they are estimates in a clinical trial population that is likely healthier and with fewer cardiovascular comorbidities compared with the real world patient; however, these rates were comparable to those found in our study [trastuzumab plus anthracyclines, 16% (95% CI, 10 to 24)]. In a retrospective cohort analysis, Bowles et al⁵³ reported a cumulative incidence of heart failure and cardiomyopathy among recipients of anthracycline and trastuzumab of 6.2% (95% CI, 4.1 to 8.2) after 1 year of follow-up, which increased to 20.1% (95% CI, 14 to 25.6) by 5 years. Thus, the duration of follow-up could also explain the different cardiotoxicity rates observed in the literature data.

Regarding the cardiotoxicity rates according to the drug regimen, we did not find a potentiation of anthracyclines cardiotoxicity when trastuzumab was also used. These results are discordant with those recently published,^{53,54} which demonstrated in large population-based retrospective cohort studies that risk of clinical cardiotoxicity, as assessed by congestive heart failure or cardiac death, was higher in patients with breast cancer who received a sequential therapy—anthracyclines followed by trastuzumab—than in those who were treated with other drug regimens. However, these studies used administrative billing codes to identify a congestive heart failure end point, usually associated with a much higher rate of cardiotoxicity. Moreover, neither our study nor our search strategy was designed to specifically evaluate the rates of cardiotoxicity according to the different drug regimens, as suggested by the relatively large CIs reported in the subgroup analysis. Thus, a potential lack of power as a result of population size and selection bias in the studies selected could have reduced the accuracy of our cardiotoxicity rates.

Fig 2. Results of a meta-analysis of the association between overweight or obesity and cardiotoxicity of anthracyclines and sequential anthracyclines and trastuzumab in patients with breast cancer. The size of the gray shaded area indicates the weight of each study. Horizontal lines show 95% CIs. D+L, DerSimonian and Leard method; M-H, Mantel-Haenzsel method; OR, odds ratio.

Obesity and Cardiotoxicity

The link between obesity and heart failure (HF) in the general population is well established. Kenchaiah et al⁵⁵ conducted the first large, epidemiologic study by analyzing 5,881 individuals from the Framingham Heart Study and showed that obesity was an independent risk factor for the development of HF. It concluded that for each increment of 1 kg/m² in BMI, there was an increase in the risk of HF of 7% for women and 5% for men.⁵⁵ The risk of developing HF was independent of age, alcohol, cigarette use, and comorbidities that included diabetes, hypertension, and a history of myocardial infarction.⁵⁶ The present unadjusted analysis is the

first to assess the potential role of overweight and obesity in cardiac dysfunction induced by anthracyclines and trastuzumab. The large population size allowed an accurate assessment of the excess risk associated with weight-related abnormalities. Obesity has been associated with a poor outcome in patients with breast cancer who were treated with anthracycline-based chemotherapy,¹⁷ affecting both overall survival and disease-free survival, and remained an important prognostic factor, independent of treatment dose.^{16,57} This, in part, could be explained by the higher rates of cardiac adverse events encountered by obese patients who are treated with anthracyclines or trastuzumab.

Fig 3. Results of a meta-analysis of the association between overweight and obesity and cardiotoxicity in patients with breast cancer who were treated with anthracyclines and sequential anthracyclines and trastuzumab. The size of the gray shaded area indicates the weight of each study. Horizontal lines show 95% CIs. D+L, DerSimonian and Leard method; M-H, Mantel-Haenszel method; OR, odds ratio.

In fact, several studies have shown that obese patients⁵⁸ or rats fed with a high-lipid diet⁵⁹ are more sensitive to the cardiotoxic effects of anthracyclines. In an *in vivo* model of overweight induced by postnatal programming, we recently demonstrated that moderately overweight adult mice were more sensitive to cardiac systolic impairment and confirmed the potentiating action of trastuzumab on doxorubicin-induced cardiotoxicity in lean mice.⁶⁰ Mechanisms by which overweight or obesity is able to promote anthracycline-induced cardiotoxicity may involve adiponectin downregulation.^{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 patients.⁶⁴ Adiponectin-KO mice showed exacerbated left ventricle contractile dysfunction after doxorubicin injection, whereas exogenous adiponectin improved doxorubicin-induced left ventricular dysfunction in wild-type and adiponectin-KO mice.⁶² However, no study has yet been performed to elucidate the role of adiponectin on trastuzumab-induced cardiac dysfunction.

Limitations

The current study has several limitations. First, it was not possible to take into account the associated cardiac risk factors or

the other classic risk factors of anthracycline and trastuzumab cardiotoxicity. Metaregressions to control for other risk factors would have required individual data for each study, which we did not obtain. Adjusted ORs were available in few studies and could not be used either; however, adjusted ORs were similar to crude ORs when they were available.^{20,40,44} Thus, the higher risk of cardiotoxicity in obese patients who were 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 cardiotoxicity. However, in unpublished data that combined breast cancer populations from two studies by Cardinale et al,^{19,20} we found that among patients with breast cancer who suffered from anthracycline and sequential anthracyclines and trastuzumab cardiotoxicity ($n = 108$), obese patients ($n = 13$) were not statistically different from normal-weight patients regarding the rates of hypertension, dyslipidemia, family history of coronary artery disease, and smoking, which thus suggested that the cardiovascular risk profile of obese patients with breast cancer was not significantly different from that of normal-weight patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Obesity As a Risk Factor for Anthracyclines and Trastuzumab Cardiotoxicity in Breast Cancer: A Systematic Review and Meta-Analysis

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Appendix

Fig A1. Funnel plot with pseudo 95% CIs. Publication bias in studies on the associations of overweight or obesity (15 studies) with cardiotoxicity of anthracyclines and sequential anthracyclines and trastuzumab. OR, odds ratio.