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EPIDEMIOLOGY

Body size and breast cancer prognosis in relation to hormone receptor and menopausal status: a meta-analysis

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Abstract Obesity is associated with poor survival after breast cancer diagnosis in individual studies and meta-analyses. Evidence regarding associations of obesity with breast cancer-specific survival (BCSS) and overall survival (OS) in relation to hormone receptor status, or BCSS in relation to menopausal status has not been evaluated in a previous meta-analysis. In this study, we conducted a meta-analysis of the association of obesity with OS and BCSS in relation to hormone receptor status and menopausal status. MEDLINE, EMBASE, and COCHRANE databases from the first record to December 2011 and presentations made at major international meetings in the last 5 years were searched. We included observational or interventional studies reporting hazard ratios (HRs) of obesity with OS and/or BCSS in relation to hormone receptor and/or menopausal status. Twenty-one studies qualified, meeting the above criteria. The pooled HR for OS in heavier versus lighter women was 1.31 (95 % CI 1.17–1.46) for estrogen receptor/progesterone receptor (ER/PgR) positive cancers; 1.18 (95 % CI 1.06–1.31) for ER/PgR negative cancers; and the difference between the two groups was not significant ($p = 0.31$). The pooled HR for OS in heavier versus lighter women was 1.23 (95 % CI 1.07–1.42) for premenopausal women and 1.15 (95 % CI 1.06–1.26) for post-menopausal women, and the difference between the two groups was not significant ($p = 0.57$). Comparable pooled HRs for BCSS were 1.36 (95 % CI 1.20–1.54) for ER/PgR positive cancers and 1.46 (95 % CI 0.98–2.19) for ER/PgR negative cancers; and 1.18 (95 % CI 0.82–1.70) for pre-menopausal women and 1.38 (95 % CI 1.11–1.71) for post-menopausal women, also without significant group differences. Results were similar after adjustment for BMI measurement technique, years of follow-up, or study design. These findings led us to conclude that there is no evidence showing that the association of obesity with breast cancer outcome differs by hormone receptor or menopausal status. This has implications for studies of weight loss interventions in the adjuvant BC setting.

Keywords Obesity · Body mass index · BMI · Breast cancer · Prognosis · Survival · Hormone receptor · ER · Menopausal

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Background

Obesity poses a major public health burden and, if the current trend continues, more than 50 % of the world's population will be obese by the year 2030 [1]. Obesity is associated with increased risk of post-menopausal breast cancer, and some reports suggest central obesity may be associated with increased risk of premenopausal breast cancer [2–4]. Numerous studies, and three recent meta-analyses, have reported an association of obesity with poor breast cancer outcomes [5–7]. The most recent meta-analysis included patients diagnosed with breast cancer as recently as 2005 and showed a modest reduction in overall survival (OS) in obese patients, an association that was

independent of menopausal status. Associations of OS with obesity in relation to hormone receptor status and that of breast cancer-specific survival (BCSS) in relation to hormone receptor and menopausal statuses were not examined; BCSS is an important outcome as it excludes obesity-associated deaths that occur as a result of non-breast cancer-related causes.

Several mechanisms for an effect of obesity on breast cancer outcomes have been proposed. Potential indirect mechanisms include presentation at a more advanced stage, chemotherapy underdosing, or an enhanced toxicity leading to reduced compliance. Direct mechanisms include hyperinsulinemia (occurring in the presence of insulin resistance), leading to activation of insulin receptor and the PI3K signaling pathway; increased inflammation; altered adipocytokine profile (increased leptin and decreased adiponectin) which can exert stimulatory effects on breast cancer cells, as well as increased levels of sex hormones such as estrogens leading to the increased signaling through estrogen receptors (ERs) [8, 9]. Obesity has been associated with increased expression of the aromatase enzyme (relevant in postmenopausal women) and with an inflammatory state in mouse models and humans [10, 11]. Furthermore, obesity has been reported to significantly influence the efficacy of treatment with aromatase inhibitors likely through influencing aromatase availability [12]. Cross-talk between growth factor (e.g., ER) and insulin signaling pathways [13] may also lead to treatment resistance and poor outcomes.

We have undertaken a series of meta-analyses to explore the associations of obesity with both OS and BCSS in relation to hormone receptor and menopausal statuses.

Methods

Search criteria

A comprehensive search of MEDLINE, EMBASE, and COCHRANE databases from the earliest record in the databases to December, 2011 was performed. Key words included POPULATION: exp Breast Neoplasms/or (exp Carcinoma/and exp breast/). EXPOSURE: body mass index (BMI)/or waist circumference/or waist-hip ratio (WHR)/or exp obesity/or body weight/or overweight. STUDY TYPES: cohort studies/or longitudinal studies/or follow-up studies/or prospective studies/or case–control studies/or retrospective studies/or cross-sectional studies. OUTCOMES: prognosis/or disease-free survival/or medical futility/or treatment outcome/or treatment failure/or disease progression/or morbidity/or incidence/or prevalence/or mortality/or cause of death/or fatal outcome/or survival rate/or survival analysis/or disease-free survival/or proportional hazards model/or exp risk. Hand searches of the reference lists of all pertinent reviews were undertaken. Presentations made at ASCO Annual Meetings, ASCO Breast Cancer Symposium, and San Antonio Breast Cancer Symposium in the last 5 years were also searched.

Identification of studies

Reports of observational or intervention studies involving newly diagnosed breast cancer populations that compared OS or BCSS in overweight and/or obese versus normal weight patients were included if they contained the following information: (i) OS and/or BCSS reported according to ER or progesterone receptor(PgR) status; and/or (ii) OS and/or BCSS reported according to menopausal status; (iii) Measurement of body size around the time of diagnosis, reported as BMI or WHR, to allow classification as overweight and/or obese versus normal weight; and (iv) explicit reporting of the hazard ratio (HR) associating body size with OS and/or BCSS. Provision of an estimate of relative risk (RR) at a single time point did not satisfy this criterion. Case-series, case reports, and other studies without a comparator, editorials, reviews, animal studies, and in vitro studies were excluded.

Data extraction

Studies were reviewed for relevance based on study design, types of participants, exposure and outcome measures. Reasons for exclusion of studies were recorded. Data were extracted using standardized data collection forms by two authors [SN and AO] independently, and any discrepancies that arose were resolved by consensus. The quality of the included studies was rated according to selection of study population, comparability of study groups, and outcome assessment based on Newcastle–Ottawa quality assessment scale [14] with modifications. When necessary, additional information was sought by correspondence with the authors of the studies.

Hormone receptor positive was defined as having positive expression of ER and/or PgR. Hormone receptor negative was defined as negative expression of both ER and PgR. Of note, most studies were conducted in the era when "low positive" (i.e., <10 % hormone receptor expression) was considered negative. OS was defined as time from breast cancer diagnosis to death from any cause, and BCSS was defined as time from diagnosis of breast cancer to death due to breast cancer or following a breast cancer-related event. HRs for the association of body size with OS and BCSS were extracted for inclusion in meta-analyses. Clinical heterogeneity of included studies was assessed before performing the meta-analysis.

Statistical analysis

Data were extracted and combined for meta-analysis using the RevMan 5.1 analysis software (The Cochrane Collaboration, Copenhagen, Denmark). Pooled estimates of HR outcomes were computed using the random-effects model [15] according to the generic inverse variance approach [16]. In this method, studies are weighted by the standard error for their individual HR rather than by sample size alone. Statistical heterogeneity was assessed by I^2 statistics [17]. Because the RevMan software cannot perform meta-regression, random effects meta-regression [18], conducted in R with the "metafor" package [19], was used to compare groups defined by hormone receptor and menopausal statuses. The sensitivity of these results to the following predefined factors: BMI ascertainment (self-reported vs investigator measured), follow-up duration (median years of follow-up $\leq$ vs >7), and study design (observation vs treatment cohort) was tested by adding each of these variables in turn to each meta-regression model as an adjusting variable. Owing to the small number of studies reporting BCSS, the sensitivity analyses were performed only for the OS outcome.

Results

Characteristics of the studies

The search strategy identified 3403 citations; 95 % of these were excluded after reviewing the title. The remaining 160 citations were retrieved and reviewed as possibly relevant. After full text review, 21 contained the required information and were included in the meta-analysis [20–41] (Fig. 1). The main reason for exclusion of studies was unavailability of HR for the association of obesity with BCSS and/or OS in defined hormone receptor or menopausal status subgroups. We identified five studies that used various methods other than HR to report association of obesity with breast cancer outcome; these were excluded from the meta-analysis [42–46]. A summary of excluded studies [43, 44, 47–75], including the reasons for exclusion, is provided in Appendix Table 2.

Characteristics of the included studies are summarized in Table 1; the quality rating of these studies is provided in Appendix Table 3. Twelve of the 21 included studies were observational cohorts, and nine were interventional studies. Sample size ranged from 177 to 14709. Meeting presentations [40] provided necessary data for three interventional studies [37–39]. Three studies were included after the authors provided additional information not included in the original publication [28, 30, 35]. All studies used BMI to characterize body size; however, the cut-point used to analyze obesity varied; the most common was $\geq$30 vs $\leq$25 kg/m^2. Body size was measured by investigators in 13 studies; in the remaining 8 studies body size was self-reported or the measurement method was not stated. Thirteen studies reported BMI associations with OS in hormone receptor positive cancers and 12 in hormone receptor negative cancers; 7 in pre-menopausal and 9 in post menopausal women. Seven studies reported the association of BMI with BCSS in ER/PgR-

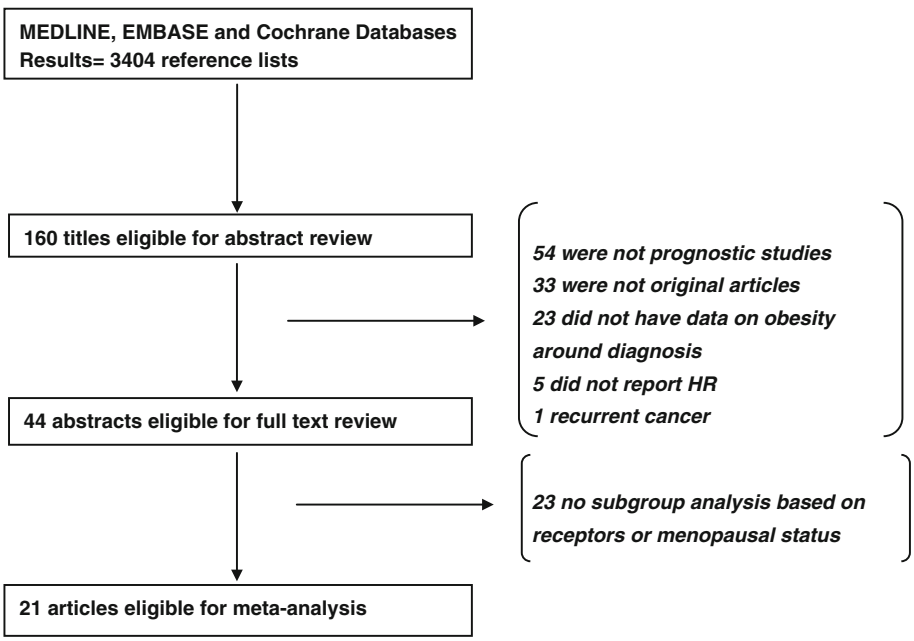

Fig. 1 Flow-chart showing search results

Table 1 Characteristics of included studies

Author (Year)	Sample size	Type of study[a]	Follow-up duration (year)	Obesity unit obesity groups	Menopause ascertainment	Adjusted variables
Azambuja (2010) [20]	2887	I	Median 5.2	BMI ≥30 vs <30	Clinical	Hormone receptor status, age, menopausal status, no. of positive lymph nodes
Berclaz (2004) [21]	6792	I	Median 14	BMI ≥30 vs ≤24.9	Clinical	Nodal status, menopausal status, ER status, PR status, tumor size, vessel invasion, tumor grade, treatment
Chang (2000) [23]	177	C	Median 8	BMI ≥30 vs ≤25	Clinical	Nodal status, treatment, Stratified by menopausal status
Chen (2010) [24]	5042	C	Median 3.84	BMI ≥30 vs 18.5–24.9	Clinical	Age at diagnosis, education, income, marital status, comorbidity, exercise participation, intake of meats, cruciferous vegetable, and soy protein, time interval from diagnosis to study enrollment, menopausal status, menopausal symptoms, surgery, chemotherapy, radiotherapy, immunotherapy, tamoxifen use, tumor-node metastasis stage, and ER/PgR status
Conroy (2011) [22]	3842	C	Median 6.2	BMI ≥30 vs 22.5–24.9	Age	Stage, hormone receptor status, smoking status
Dal Maso (2008) [25]	1453	C	Median 12.6	BMI ≥30 vs ≤25	Clinical	Age, stage, ER & PR status
Dignam (2003) [26]	3385	I	Median 13.8	BMI ≥30 vs 18.5–24.9	Clinical	Treatment, age, menopausal status, race, tumor size, ER level, PR level
Dignam (2006) [27]	4077	I	Median 14	BMI ≥30 vs ≤25	Clinical	Age, race, tumor size
Daling (2001) [28]	1177	C	Median 10	BMI ≥25.8 vs ≤20.6	Age	Age, year of diagnosis
Davidson (2005) [38]	1501	I	Median 9.6	BMI ≥30 vs unclear comparator	Clinical	Age, tumor size, nodal status, race, surgery type, prior radiation therapy, menopausal status, treatment arm, and treatment adherence
Enger (2004) [29]	744	C	Median 10.4	BMI ≥25 vs ≤20.4	Age	Age, stage at diagnosis, physical activity
Fetting (1998) [39]	610	I	Median 3.98	BMI ≥30 vs unclear comparator	Unclear	Age, tumor size, nodal status, race, surgery type, prior radiation therapy, menopausal status, treatment arm, and treatment adherence
Goodwin (2002) [30]	512	C	Median 4	BMI ≥30 vs 18.5–24.9	Clinical	No adjustments made. Excluded women with diabetes from study
Keegan (2010) [31]	4153	C	Median 7.8	BMI ≥25 vs <25	Unclear	Site, age of diagnosis, race, time since last full-term pregnancy, number of affected nodes, ER/PR status, tumor grade, tumor size, and tumor type
Kwan (2011) [32]	14948	C	Mean 7.8	BMI ≥25 vs 18.5–24.9	Unclear	Age at diagnosis, AJCC stage, race/ethnicity, education, menopausal status, hormone receptor status, surgery, chemotherapy, radiation therapy, hormonal therapy, smoking, comorbidity, and physical activity

Table 1 continued

Author (Year)	Sample size	Type of study[a]	Follow-up duration (year)	Obesity unit obesity groups	Menopause ascertainment	Adjusted variables
Loi (2005) [33]	1101	C	Median 5	BMI ≥30 vs ≤25	Clinical	Age, tumor grade, nodal status, PR status
Majed (2008) [34]	14709	C	Median 20	BMI ≥30 vs ≤25	Unclear	Age, tumor size, nodal status, year of diagnosis, ER & PR status, tumor grade
Sparano (2010) [40]	3484	I	Median 5.3	BMI ≥30 vs unclear comparator	Age	Age, tumor size, nodal status, race, surgery type, prior radiation therapy, menopausal status, treatment arm, and treatment adherence
Sestak (2010) [41]	5172	I	Median 8.33	BMI ≥30 vs ≤23	Clinical	Age, region, chemotherapy, radiotherapy, mastectomy, tumor size, tumor grade, and nodal status
Vitolins (2008) [35]	636	I	Median 13.7	BMI >30 vs <30	Clinical	Reported 5 and 10 year survival stratified by age, ER status, PR status, menopausal status, number of positive nodes
Whiteman (2005) [36]	3924	C	Median 14.6	BMI ≥30 vs ≤23	Clinical	Age at diagnosis, race, radiation therapy, history of benign breast disease, education, stage

[a] *I* Interventional, *C* observational cohort, *BMI* body mass index

positive patients, 6 in ER/PgR-negative patients, 4 in pre-menopausal patients and 4 in post-menopausal patients. Median follow-up was less than 5 years in three studies (around 4 years), between 5 and 10 years in 10 studies and more than 10 years in 8 studies. Assessment of publication bias using techniques such as funnel plot was not done because of the small number of studies in each category.

Overall survival in relation to obesity

The pooled HR for the association of obesity (vs no obesity) with OS in hormone receptor positive breast cancer (Fig. 2) was 1.31 [95 % CI 1.17–1.46] in the 13 studies reporting this association. The pooled HR for the association of obesity (vs no obesity) with OS in hormone receptor negative breast cancer was 1.18 [95 % CI 1.06–1.31] in the 12 studies reporting this association. The combined HR was 1.25 (95 % CI 1.16–1.35). There was no evidence that the association of obesity with OS differed in hormone receptor positive and hormone receptor negative cancers ($p = 0.31$) and this did not change after adjusting in turn for BMI measurement technique, years of follow-up, and study design (receptor status $p = 0.33$, 0.25, 0.31, respectively, after adjustment). Similarly, HR for OS was 1.23 (95 % CI 1.07–1.42) for premenopausal women in seven studies reporting this association and 1.15 (95 % CI 1.06–1.26) for post-menopausal women in nine studies that reported this association (Fig. 3). The combined HR was 1.19 (95 % CI 1.10–1.28). There was no evidence of sub-group difference in association of OS with obesity between pre and post menopausal women ($p = 0.57$), and this did not change after adjusting in turn for BMI measurement technique, years of follow-up, and study design (receptor status $p = 0.64$, 0.33, and 0.64, respectively, after adjustment).

Breast cancer-specific survival in relation to obesity

The pooled HR for the association of obesity (vs no obesity) with BCSS in hormone receptor positive breast cancer was 1.36 [95 % CI 1.20–1.54] in the 7 studies examining this association. The pooled HR for the association of obesity (vs no obesity) with BCSS in hormone receptor negative breast cancer was 1.46 [95 % CI 0.98 to 2.19] in the 6 studies reporting this association. There was no evidence that these associations differed in hormone receptor positive and negative cancers ($p = 0.95$). HRs for the association of obesity (vs no obesity) with BCSS were 1.18 [95 % CI 0.82–1.70] in pre-menopausal women (4 studies) and 1.38 [95 % CI 1.11–1.71] in post-menopausal women (4 studies). There was no evidence that these associations differed in pre-and postmenopausal women ($p = 0.35$) (Figs. 4, 5).

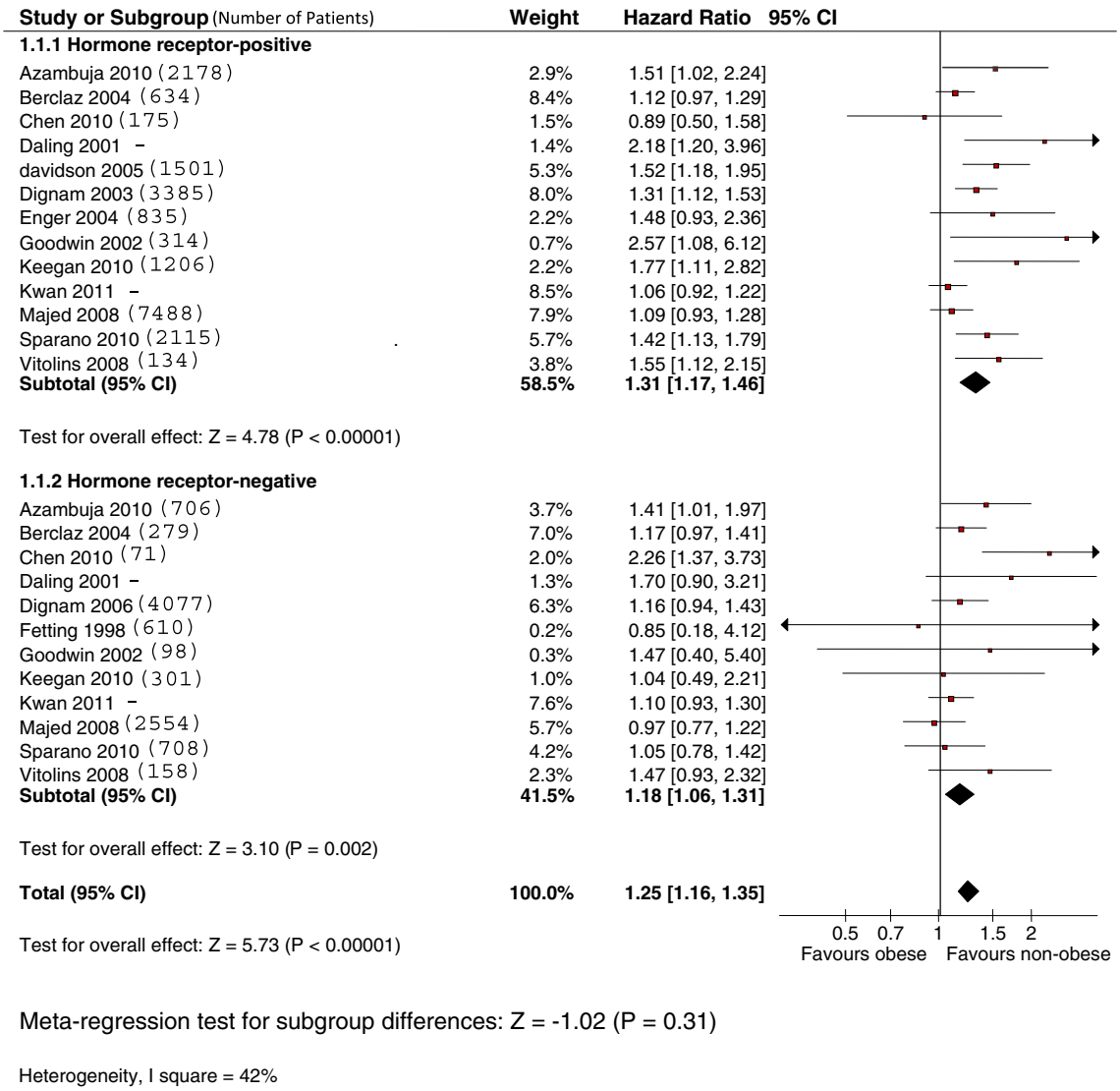

Fig. 2 Pooled analysis of overall survival (OS) in obese versus non-obese women with breast cancer according to hormone receptor status

Discussion

Although obesity has been associated with poor OS in previous studies, our meta-analysis is the first to our knowledge to demonstrate that the association of obesity with poor OS and that BCSS do not appear to differ in hormone receptor positive (vs hormone receptor negative) breast cancer (p for differences of 0.31 and 0.95, respectively).

Our finding that the decrease in OS and BCSS in those patients with obesity appears unrelated to the expression of hormone receptors is not consistent with the observation that a dietary intervention that was designed to reduce fat intake (and was also associated with modest weight loss) may have had a greater effect on relapse-free survival in women with ER/PR negative breast cancer than in those with ER/PR positive breast cancer (HR 0.44, 95 % CI 0.25–0.77 and HR 0.83, 95 % CI 0.58–1.17, respectively, interaction $p = 0.15$) [76]. This inconsistency may reflect the nature of the dietary fat intervention used in this study (as opposed to a weight loss intervention) or the play of chance (the interaction was not significant); it is also possible the pattern of prognostic associations of obesity at diagnosis may not predict which subgroups will benefit from weight loss interventions. From a biological point of view, our failure to identify differential effects of obesity in hormone receptor positive and negative breast cancers suggest that pathways not related to sex hormones, such as insulin or insulin-like growth factor (IGF) signaling pathways, may contribute to effects of obesity on breast cancer outcomes.

Our observation of a lack of evidence that the association of obesity with poor OS and BCSS differ by hormone

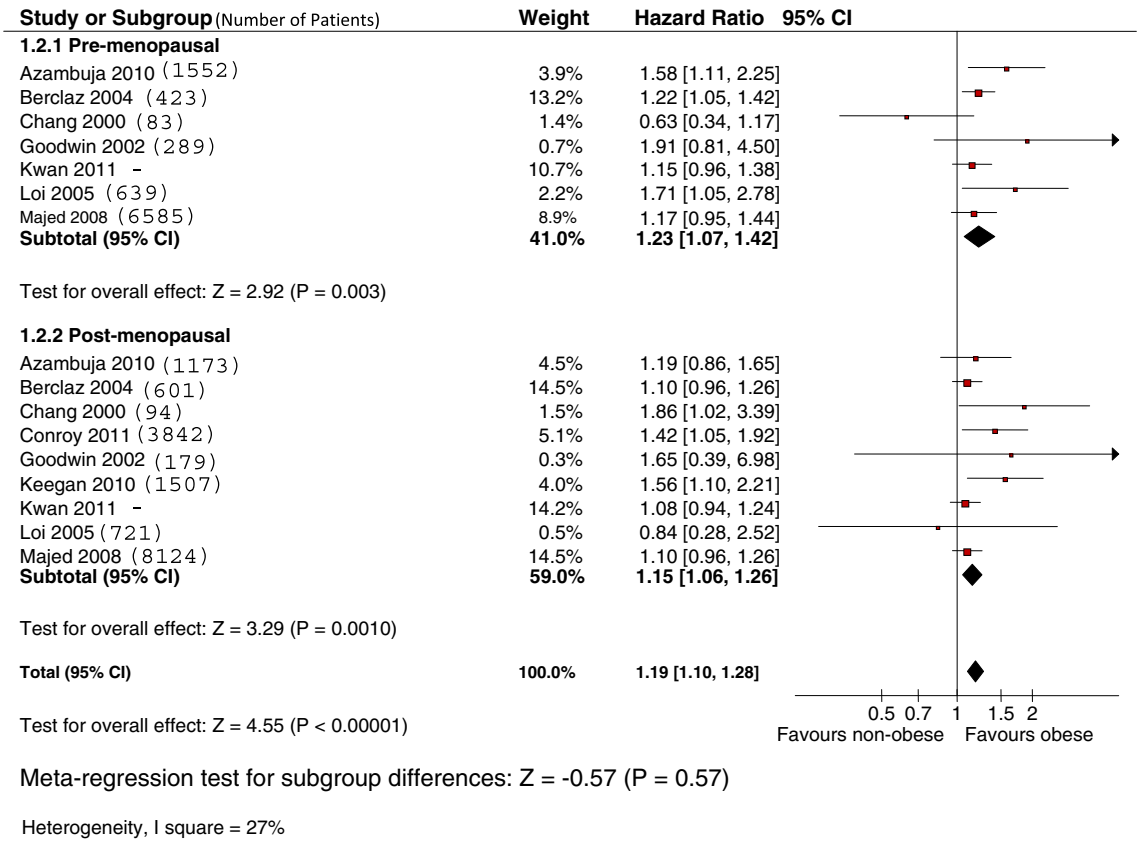

Fig. 3 Pooled analysis of overall survival in obese versus non-obese women with breast cancer according to menopausal status

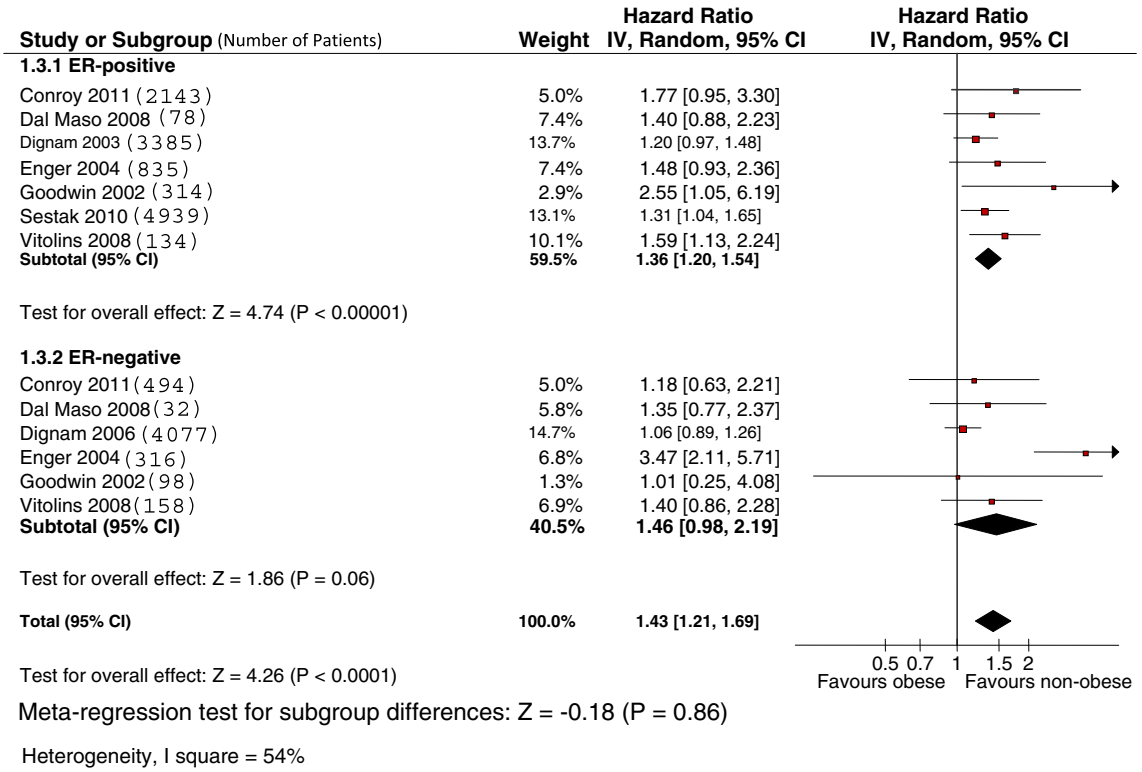

Fig. 4 Pooled analysis of breast cancer-specific survival in obese versus non-obese women according to hormone receptor status

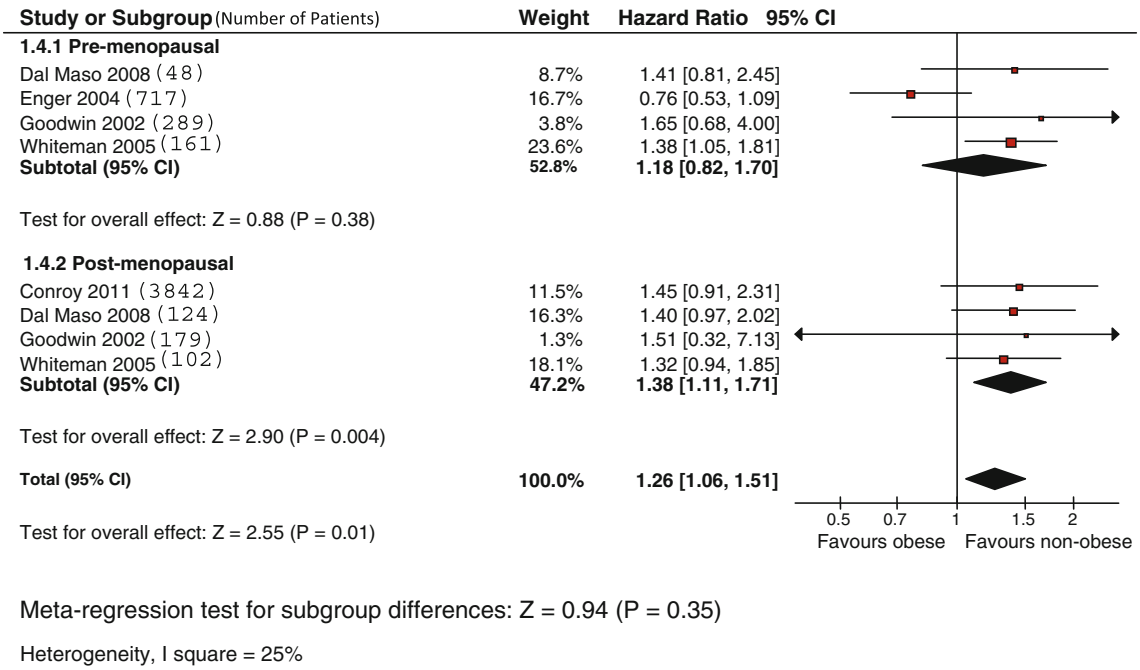

Fig. 5 Pooled analysis of breast cancer-specific survival in obese versus non-obese women according to menopausal status

receptor ($p = 0.31$ and 0.95, respectively) and menopausal status ($p = 0.57$ and 0.35, respectively) extends results of a previous meta-analysis reported by Protani et al. [6] that reported the association of menopausal status relation to OS but did not explore association of hormone receptor status on OS and BCSS or menopausal status on BCSS. In addition, we included more recent studies and exclusively limited our analysis to studies reporting the interaction of hormone receptor and/or menopausal status in association of obesity to outcome of breast cancer. Nevertheless, the overall effect size HRs for OS and BCSS in obese versus non-obese patients obtained in our study are comparable to that obtained by Protani et al.

Our observation that obesity is associated with poor BCSS (in addition to OS) suggests that prognostic associations of obesity are not due to death from causes other than breast cancer in overweight and/or obese patients. Our analyses of potential effects of the method of BMI ascertainment (investigator vs self-report), duration of follow-up, and study type (interventional vs observational) suggest that our findings were robust to the methodology used in the included studies.

The association of obesity with breast cancer outcomes is complex, and its underlying basis is likely multi-factorial. Although indirect causes, such as diagnosis at a more advanced stage or inadequate treatment of obese patients may contribute in some patients, poorer outcomes in obese women have been reported after these factors have been considered. Increased adiposity is associated with higher aromatase activity and higher estrogen levels in postmenopausal women and higher estrogen levels have been associated with worse breast cancer outcomes in this group [77]—it has also been suggested that a higher aromatage inhibitor dose be used in obese post-menopausal women with breast cancer [41]. However, obesity-associated estrogen levels are unlikely to be important mediators of obesity effects in premenopausal women (in whom most of the estrogen is derived from the ovaries), in women with hormone receptor negative breast cancer, or in those receiving tamoxifen. Emerging mechanistic research [78–80] in the clinical and preclinical settings has identified a group of obesity-associated physiologic factors associated with poor breast cancer outcomes and having plausible biologic mechanisms. These include higher circulating levels of insulin (and possibly IGFs), greater systemic and/or local inflammation and altered adipocytokines (higher leptin and lower adiponectin). High levels of insulin or c-peptide have been established to be associated with poor cancer outcomes [81–86]. Non-diabetic women with insulin levels in the highest (vs lowest) quartile have a doubled risk of recurrence and tripled risk of death, effects that persist after consideration of tumor and treatment-related factors [30]. Evidence exists, although less strong, for the other factors. Many of these

physiologic disruptions occur together as part of the obesity-associated insulin resistance syndromes [87]. Our recent observation [88] that insulin may be most important early after diagnosis (first 5 years) and leptin may be more important long term underscores the complexity of obesity effects in breast and other cancers and highlights the need for additional research.

Strengths of our research include the broad literature search process, the evaluation of study quality, and the restriction of our analyses to pre-specified associations and subgroups. Obese and non-obese patients were fairly comparable in all studies. Major confounding factors such as age, stage (or nodal status), tumor size, and treatment received were adjusted for in most studies (Table 1). The ascertainment of outcome was through record linkage or direct inquiry in all the studies except in one where authors did not report on how the survival data were collected [34]. Follow-up duration was adequate in the majority of the studies. Losses to follow-up was reported and were acceptable (<20 %) when reported (5 studies). Finally, included studies were carried out in diverse locations around the world and included a variety of population of breast cancer contributing to generalizability of the results.

Limitations of our research include our analysis of published study-level data, rather than analysis of patient-level data. In addition, most included studies were not specifically designed to examine prognostic effects of obesity—as a result of which body size was often obtained through self-report, and it was not clear whether it was measured with the same rigor in all studies. Differences in categorizing obesity across studies likely contributed to heterogeneity in our meta-analysis. Two studies used populations that were highly selective sub-groups of breast cancer patients [26, 27], and this might have compromised the generalizability of our results. The failure of the majority of studies that have examined the association of obesity with breast cancer outcomes to report associations by menopausal or hormone receptor status reduced the number of studies that could be included in our meta-analyses, lowered the power, might have introduced bias, and thereby reduced generalizability of our findings. The lack of statistically significant differences, especially for BCSS, might reflect lower power rather than the absence of a real effect. Our meta-analysis is prone to biases that were present in the parent studies [89]. In addition, differing approaches in the management of breast cancer patients by hormone receptor and/or menopausal status may have confounded the associations we identified. Most included studies were from the era when expression of <10 % of ER or PR was considered negative; this differs from current practice. Finally, our study focused on baseline BMI which is likely to vary over time, and the effect of change in BMI to prognosis of breast cancer is not captured in our analysis. This is particularly important as there are concerns regarding adverse prognostic implications of change in BMI after diagnosis of breast cancer [48, 90]. In addition, evidence suggests that a very low BMI with breast cancer has a worse prognosis as compared with their normal weight counterparts [91, 92]; evaluation of such effect through this study is outside the scope of this analysis.

In summary, our results did not find evidence that the associations of obesity with either BCSS or OS differ by the menopausal status of the patient or the hormone receptor status of the cancer. Any differences that exist are likely to be quantitative rather than qualitative, based on the HRs we have observed. Our findings are consistent with a contribution of non-estrogenic mediators, such as insulin, inflammation, or altered adipokine profiles, to prognostic effects of obesity. Additional research is needed to investigate these mediators, in addition to estrogens. Our findings have relevance for future research in that they suggest intervention trials targeting weight loss or that physiologic mediators of obesity should include both hormone receptor positive and negative cancers and both pre-and postmenopausal women.

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Conflict of interest This is to confirm that none of the authors of the above manuscript have conflict of interest of any kind which may arise from being named as an author on the manuscript.

It is to certify that (i) all financial support or benefits received by me, by any member of my immediate family, or any individual or entity with whom or with which I have a significant relationship from any commercial source related directly or indirectly to the scientific work reported in the article have been disclosed and have been included in the submitted manuscript, (II) neither I, nor any member of my immediate family, nor any individual or entity with whom or with which I have a significant relationship has a financial interest in the subject matter discussed in the manuscript, except as disclosed (I understand an example of such a financial interest would be a stock interest in any business entity which is included in the subject matter of the manuscript or which sells a product relating to the subject matter of the manuscript.), (III) all funding sources supporting the work and all institutional or corporate affiliations are acknowledged in a footnote, and (Iv) I have had full access to all the data in the study (if applicable) and thereby accept full responsibility for the integrity of the data and the accuracy of the data analysis.

Signed by: Saroj Niraula, Alberto Ocana, Marguerite Ennis and Pamela J. Goodwin

Appendix

See Tables 2 and 3.

Table 2 Quality rating of the included studies according to modified Newcastle–Ottawa quality assessment scale

Author year	Assessment of selection bias			Comparability (adjustment/matching)		Outcome		
	Exposed representation (★= no major bias)	Non-exposed selection (★= no major bias)	Ascertainment of obesity (★= investigator-measured)	Nodal status or stage (★= adjusted)	Age (★= adjusted)	Assessment/ ascertainment (★= no major bias)	Followup length (★= median ≥5yr)	Attrition (★ = adequate)
De Azambuja 2010[20]	★	★	★	★	★	★	★	★
Berclaz 2004[21]	★	★	★	★	★	★	★	
Conroy 2011[22]			★	★		★	★	
Chang 2000[23]			★	★	★	★	★	
Chen 2010[24]	★	★	★	★	★	★		
Dal Maso 2008[25]	★	★		★	★	★	★	★
Dignam 2003[26]			★	★	★	★	★	
Dignam 2006[26]			★	★	★	★	★	
Daling 2001[28]	★	★			★	★	★	
Enger 2004[29]	★	★		★	★	★	★	★
Goodwin 2002[30]		★	★	★	★	★		★
Keegan 2001[31]	★	★		★	★	★	★	
Kwan 2011[32]	★	★		★	★	★	★	★
Loi 2000 [33]	★	★		★	★	★	★	
Majed 2008[34]	★	★	★	★	★		★	
Sestak 2010 [41]	★	★	★	★	★	★	★	★
Vitolins 2008[35]	★	★	★	★	★	★	★	★
Whiteman 2005[36]	★	★			★	★	★	

Three studies from meeting presentations are not rated

Table 3 List and short description of excluded studies (only those that could potentially be included are listed)

Author (Year)	Description of studies
Demirkan (2007) [43]	This study performed in Turkish women with early breast cancer only reported disease-free survival and distant disease-free survival in obese versus non-obese women
Jain (2005) [47]	This was a secondary analysis of Canadian randomized trial, the National Breast Screening Study (NBSS). Outcomes were not limited to participants who developed breast cancer
Kroenke (2005) [48]	This large prospective cohort study was designed to study weight and weight gain after diagnosis of breast cancer to its outcome. Adjusted risk ratio for breast cancer mortality in obese as compared to non-obese women were was 2.02 (95 % CI 1.13–3.61) for pre-menopausal women and 0.88(95 % CI 0.61–1.28) for post-menopausal women. It used unvalidated method to report recurrence and patient's self-reported BMI
DenTonkelaar (1995) [49]	It is a prospective study that included women in Netherland with a mean follow-up of over 9 years. The outcome was reported in incidence density ratio and showed no significant association between obesity and breast cancer outcome
Maehle (1996) [44]	This is a study from a particular geographic area in Norway. It concludes that obesity is associated with more deaths in breast cancer with positive hormone receptors whereas non-obese people have increased risk of death in non-obese population. This study has major limitations such as purely retrospective nature of the study, vital statistics were captured more than 12 years before breast cancer diagnosis and hormone receptor status was ascertained much later than time of diagnosis

Following studies reported data on association of obesity with either overall or breast cancer-specific survival, but none reported data on the interaction on the basis of hormone receptor status and menopausal status. The respective authors were contacted, who indicated non-availability of such data

Abrahamson (2006) [50]	Barnett (2008) [51]	Bastarrachea (1994) [52]	Borugian (2003) [53]	Caan (2008) [54]	Carmichael (2004) [55]
Cleveland (2007) [56]	Dawood (2008) [57]	Eley (1994) [58]	Greenberg (1985) [59]	Hebert (1998) [60]	Holmberg (1994) [61]
Katoh (1994) [62]	Labidi (2008) [63]	Litton (2008) [64]	Mason (1990) [65]	Moon (2009) [66]	Newman (1997) [67]
Nichols (2009) [68]	Petrelli (2002) [69]	Pierce (2007) [70]	Reeves (2000) [71]	Rosenberg (2009) [72]	Saxe (1999) [73]
Tao (2006) [74]	Vatten (1991) [75]				

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