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CLINICAL TRIAL

Obesity as an independent risk factor for decreased survival in node-positive high-risk breast cancer

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Abstract Obese breast cancer patients have a higher risk of lymph node metastasis and a poorer prognosis compared to patients with normal weight. For obese women with node-positive breast cancer, an association between body weight and prognosis remains unclear. In this retrospective study, we analyzed patient data from the Phase-III ADE-BAR trial, in which high-risk breast cancer patients (pT1–4, pN2–3, pM0) were randomized into a docetaxel-based versus epirubicin-based chemotherapy regimen. Patients were grouped according to their BMI value as underweight/normal weight (BMI < 25 kg/m^2; $n = 543$), overweight (BMI 25–29.9 kg/m^2; $n = 482$) or obese (BMI ≥ 30 kg/m^2; $n = 285$). Overweight and obese patients were older, had larger tumors and were more likely to be postmenopausal at the time of diagnosis compared to underweight/normal-weight patients (all $p < 0.001$). Multivariate Cox regression analyses adjusting for age and histopathological tumor features showed that obese patients had a significantly shorter disease-free survival (DFS; HR 1.43; 95 % CI 1.11–1.86; $p = 0.006$) and overall survival (OS; HR 1.56; 95 % CI 1.14–2.14; $p = 0.006$) than non-obese patients. Subgroup analyses revealed that the differences in DFS and OS were significant for postmenopausal but not for premenopausal patients, and that the survival benefit of non-obese patients was more pronounced in women with hormone-receptor-positive disease. Obesity constitutes an independent, adverse prognostic factor in high-risk node-positive breast cancer patients, in particular for postmenopausal women and women with hormone-receptor-positive disease.

Keywords Node-positive breast cancer · Obesity · Outcome

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Introduction

Obesity is a major risk factor for morbidity throughout the world [1] and is associated with an increased risk of mortality due to diabetes and kidney diseases, coronary heart disease, and other cardiovascular ailments [2]. Obesity has also been linked to an increased incidence of cancer and cancer mortality [2, 3]. Several studies have investigated the association between body weight or body mass index (BMI) and breast cancer incidence, and there is convincing evidence that overweight or obese postmenopausal women have an increased risk of breast cancer as compared to normal-weight women [4, 5]. However, the

available data for premenopausal women are less clear and several large studies or meta-analyses found no significant relationship between BMI and breast cancer risk or even an inverse association with overweight or obese premenopausal women having a reduced breast cancer risk [6].

In addition to other mechanistic links, it has been established that excess estrogen levels contribute to the development of breast cancer in obese women [7, 8], and multiple studies have shown that the association between obesity and breast cancer risk is especially pronounced for hormone-receptor-positive breast cancer. However, positive associations between obesity and breast cancer risk have also been demonstrated for triple-negative breast cancer [9, 10].

Overweight and obesity are not only linked to breast cancer incidence, but women that are obese at the time of breast cancer diagnosis also have worse outcomes compared to normal-weight patients in terms of recurrence and survival [11, 12]. However, most studies investigating the relationship between BMI and recurrence or survival are based on patients with either very heterogeneous tumor characteristics or early stage low-risk breast cancer, while very few data exist on the specific impact of obesity on prognosis for high-risk breast cancer patients. Therefore, we analyzed BMI and outcome data from node-positive breast cancer patients (pT1–4, pN2–3, pM0) that were recruited in a clinical trial involving exclusively women with high-risk breast cancer, the German ADEBAR trial. The aim of our study was to investigate the association between BMI at time of diagnosis, baseline histopathological tumor characteristics and outcome in terms of disease-free survival (DFS) and overall survival (OS). In addition, we performed subgroup analyses with respect to menopausal status and hormone receptor status, which are the two factors most likely to affect the relationship between BMI and outcome in breast cancer patients.

Patients and methods

The ADEBAR study is a prospective, randomized, multicenter Phase-III trial with the primary endpoint of DFS in high-risk breast cancer patients (defined as >4 cancerous lymph nodes). This study involves randomizing a sequential anthracycline-docetaxel regimen (Treatment arm A: EC-Doc: 4 cycles of epirubicin (E) 90 mg/m^2 BSA plus cyclophosphamide (C) 600 mg/m^2 BSA q21d, followed by 4 cycles of docetaxel (D) 100 mg/m^2 BSA q21d) against an anthracycline-containing standard chemotherapy (Treatment arm B: FEC120: 6 cycles of E60 mg/m^2 BSA d 1 + 8, 5- fluorouracil 500 mg/m^2 BSA d 1 + 8 und C 75 mg/m^2 BSA d 1−14, q28d). Secondary endpoints include OS, chemotherapy-toxicity, and quality of life.

Patients and recruitment

Between September 2001 and May 2005, 1493 women between the age of 18 and 70 years with completely resected, lymph node-positive primary breast cancer (pT1–4, pN2–3, pM0) were randomized (748 in treatment arm A and 745 in treatment arm B) in the ADEBAR trial after signing an informed consent form. Patients suffering from metastatic, inflammatory breast cancer or other primary malignancies were not included. Additionally, pregnant or lactating patients or those with known cardiac disorders or hypersensitivity to any of the study medications were excluded. Of the 218 registered study centers, 198 (91 %) actively participated in patient recruitment. Body weight was measured using a calibrated scale under standardized conditions, height was measured to the nearest 0.5 cm. BMI was calculated as weight in kg divided by the square of height in meter.

Endocrine treatment

Patients who had hormone-receptor-positive breast cancer (estrogen and/or progesterone receptor levels ≥10 %) received tamoxifen (20 mg/dpo), while postmenopausal patients with a contraindication to tamoxifen were given an anti-aromatase agent for 5 years. Patients with a positive hormone receptor status that were under 40 years of age, menstruated within 6 months after completing chemotherapy, or exhibited levels of LH < 20 mI U/ml, FSH < 20 mI U/ml and E2 > 20 pg/ml also received goserelin (3.6 mg q1 msc) for 2 years.

Data analysis

Overall, data on survival and BMI were available for 1310 of the 1493 randomized patients (see CONSORT diagram, Fig. 1). Data from both randomization arms were pooled for an explorative retrospective analysis to study the relationship between BMI at baseline and survival. Patients were grouped according to the following World Health Organization (WHO) criteria for BMI: underweight, <18.5 kg/m^2 (n = 13); normal weight, 18.5–24.9 kg/m^2 (n = 530); overweight, 25.0–29.9 kg/m^2 (n = 482); and obese, ≥30.0 kg/m^2 (n = 285). Due to the low number of patients with a BMI below 18.5, underweight and normal-weight patients were combined into one group for further analyses (underweight/normal weight, n = 543).

Patient outcome was analyzed in terms of both DFS (with local, contralateral, and distant disease recurrence as well as secondary primary tumors and death from any cause defined as event) and OS (with death from any cause defined as event). The time-to-event intervals were measured from the date of randomization to the date of the

Fig. 1 CONSORT diagram for the explorative retrospective analysis of the relationship between baseline body mass index and survival in patients randomized for the ADEBAR trial
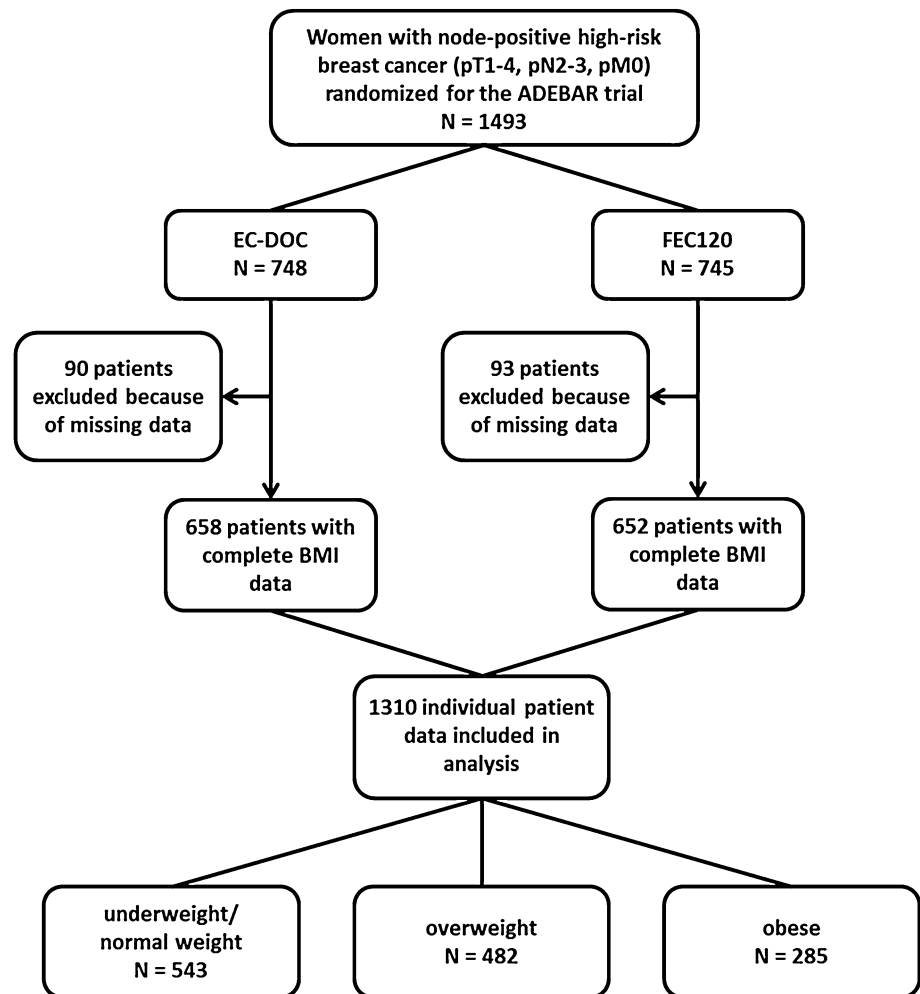
event. Data were censored at the date of the last adequate follow-up in case no event was reported. Median follow-up was 60.6 months.

Statistical analyses were performed using SPSS software, version 19 (SPSS Inc., Chicago, IL, USA). Descriptive statistics for categorical data were summarized using frequency tables presenting absolute and relative frequencies. Associations between BMI group and patient or tumor characteristics were evaluated using Chi Square tests. Survival estimates were obtained using the Kaplan–Meier product limit method and survival curves were compared using log-rank tests. Effects of multiple covariates on survival endpoints were calculated using Cox proportional hazards regression models. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

To analyze whether BMI group constitutes an independent prognostic factor for DFS and OS, we used Cox proportional hazards regression models adjusted for age class ($\leq$40, 41–50, 51–60, >60), menopausal status (premenopausal, postmenopausal), tumor stage (pT1, pT2, pT3, pT4), nodal stage (pN2, pN3), histological grading (G1, G2, G3), histological type (ductal, lobular, other), hormone receptor status (positive, negative), Her2 status (positive, negative), and chemotherapy treatment (EC-Doc, FEC120). Effects of multiple covariates on survival endpoints were calculated using Cox proportional hazards regression models.

Results

Association of BMI with baseline patient and tumor characteristics

No significant differences were found between BMI groups (underweight/normal weight, overweight, obese) with regard to the histopathological tumor features nodal stage, tumor grade, histological subtype, hormone receptor status, and Her2 receptor status (see Table S1). In addition, patients in the three BMI groups were equally likely to receive either the EC-Doc or the FEC120 chemotherapy

(Table S1). However, the BMI category was significantly associated with tumor size, age, and menopausal status. Both overweight and obese patients had larger tumors (more pT3 and pT4 tumors and less pT1 tumors) as compared to underweight/normal-weight patients (Table S1). Furthermore, overweight and obese patients were older at the time of primary diagnosis than underweight/normal-weight patients, as patients with a BMI exceeding 25.0 kg/m^2 were more often 60 years or older and less often younger than 50 years compared to patients with a BMI under 25.0 kg/m^2 (Table S1). Finally, the BMI groups differed significantly with regard to menopausal status. Nearly half of the women (47.3 %) in the underweight/normal-weight subgroup were premenopausal, whereas only 30.7 and 28.8 % of the women were premenopausal in the overweight and obese subgroup, respectively (Table S1).

BMI and outcome

Overall, 362 (27.6 %) patients showed disease recurrence, and median DFS was 105.1 months (95 % CI 101.9–108.3 months). There were significant differences in DFS among the three BMI groups (log-rank test; $p = 0.004$; see Fig. 2a). Median DFS was 104.5 months (95 % CI 100.0–109.1 months) for underweight/normal-weight patients (140 events, 25.8 %) and 77.2 months (95 % CI 69.0–85.3 months) for obese patients (98 events, 34.4 %), while median DFS was not reached in our study for overweight patients (124 events, 25.7 %). Pairwise comparisons using log-rank tests revealed that both underweight/normal-weight patients ($p = 0.004$) and overweight patients ($p = 0.003$) had better survival prospects in terms of prolonged DFS as compared to obese patients, while there was no significant difference regarding DFS between underweight/normal-weight and overweight patients ($p = 0.788$). Based on these results, we combined all patients with a BMI below 30 (non-obese) and performed a multivariate Cox regression analysis to test whether the parameter

BMI group (obese vs. non-obese) had prognostic relevance for DFS independently from other well-known prognostic factors. The multivariate analysis confirmed that obesity was an independent prognostic factor for poor DFS, with a hazard ratio (HR) of 1.43 (95 % CI 1.11–1.86; $p = 0.006$; see Table S2).

225 patients died during follow-up. Similar to DFS, there were significant differences in OS among BMI groups (log-rank test; $p = 0.004$; see Fig. 2b). Again, both underweight/normal-weight patients and overweight patients had significantly prolonged OS as compared to obese patients ($p = 0.001$ and 0.019, respectively), while there was no significant difference regarding OS between underweight/normal-weight and overweight patients ($p = 0.345$). A multivariate Cox regression showed that obesity (obese vs. non-obese) was an independent predictor of poor OS (HR 1.56; 95 % CI 1.14–2.14; $p = 0.006$; see Table S3).

Effect of menopausal status

We performed separate analyses to compare DFS and OS between obese and non-obese patients for premenopausal and postmenopausal women. The corresponding survival plots are shown in Fig. 3. Both DFS and OS were significantly different between obese and non-obese postmenopausal patients (log-rank test; $p = 0.002$ and 0.001, respectively), while there were no significant differences regarding DFS and OS between obese and non-obese premenopausal patients (log-rank test; $p = 0.325$ and 0.524, respectively). The results of these univariate analyses were confirmed by multivariate Cox regressions adjusting for age, and histopathological tumor characteristics. Obese postmenopausal patients had a significantly shorter DFS (HR 1.56; 95 % CI 1.15–2.12; $p = 0.004$) and OS (HR 1.79; 95 % CI 1.25–2.58; $p = 0.002$) than non-obese postmenopausal women. In contrast, the multivariate Cox regression revealed no differences in DFS or OS between

Fig. 2 Kaplan–Meier plots of disease-free survival (**a**) and overall survival (**b**) according to BMI group (underweight/normal, overweight, obese)
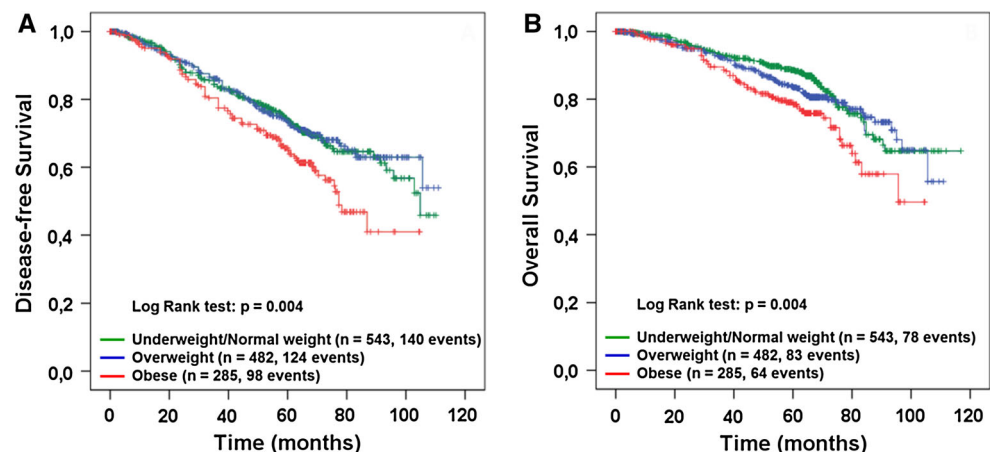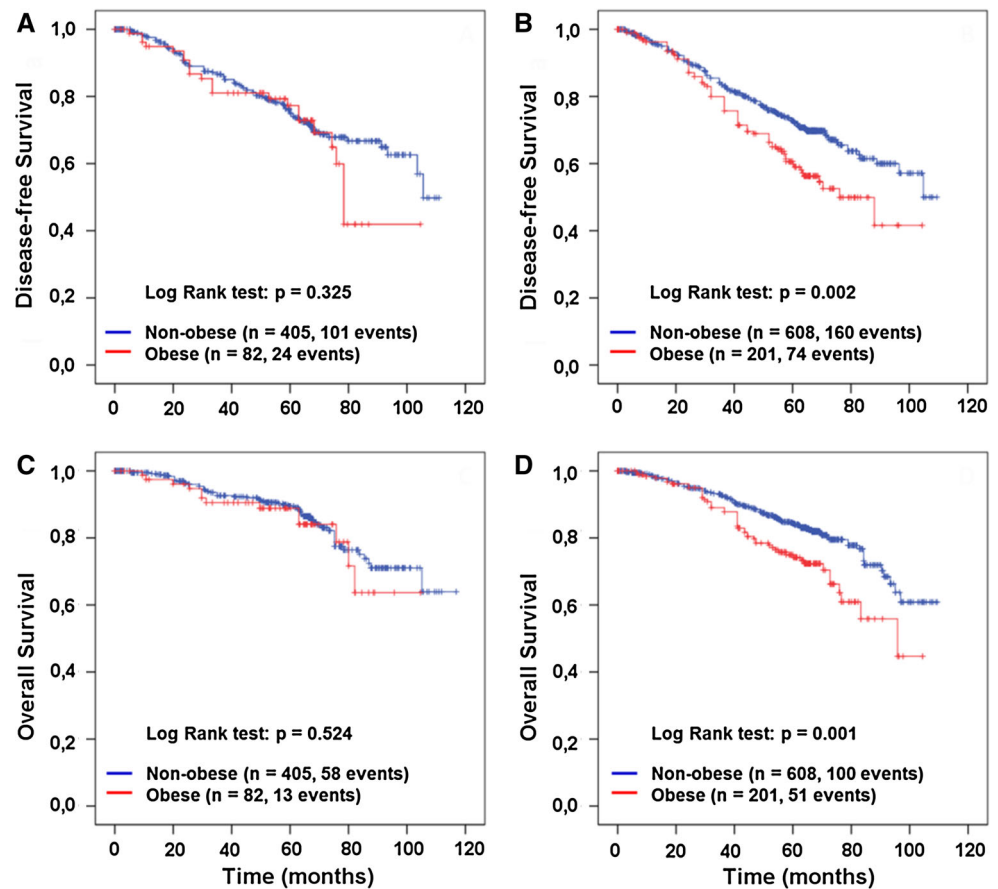
Fig. 3 Kaplan–Meier plots according to BMI group (non-obese, obese) of disease-free survival in premenopausal (**a**) and postmenopausal (**b**) patients, and of overall survival in premenopausal (**c**) and postmenopausal (**d**) patients

obese and non-obese premenopausal patients (DFS: HR 1.06; 95 % CI 0.63–1.76; $p = 0.84$; OS: HR 0.94; 95 % CI 0.46–1.89; $p = 0.853$).

Effect of hormone receptor status

To assess whether the association between BMI and outcome was affected by hormone receptor status, we compared DFS and OS between obese and non-obese women separately for patients with a hormone-receptor-positive and patients with a hormone-receptor-negative tumor. Kaplan–Meier survival plots are shown in Fig. 4.
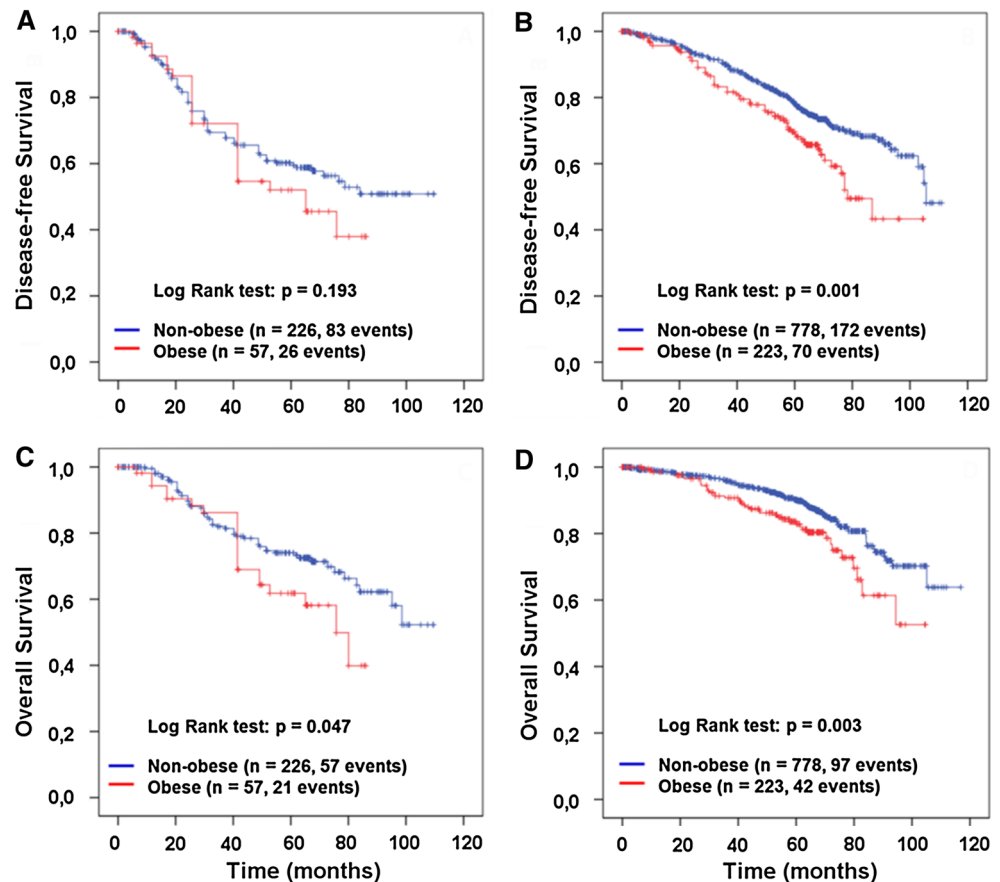
Log-rank tests revealed that obese women with hormone-receptor-positive breast cancer had a significantly worse DFS and OS compared to non-obese women with hormone-receptor-positive breast cancer ($p = 0.001$ and 0.003, respectively). Multivariate Cox regressions confirmed these results for DFS (HR 1.53; 95 % CI 1.12–2.09; $p = 0.007$), but failed to show a significant prolonged OS in non-obese as compared to obese women with hormone-receptor-positive tumors, though the hazard ratio was similar as for DFS and statistical significance was borderline (HR 1.48; 95 % CI 0.99–2.21; $p = 0.057$).

In women with hormone-receptor-negative tumors, both univariate log-rank tests and multivariate Cox regressions showed no difference in DFS between obese and non-obese women (log-rank test: $p = 0.193$; Cox regression: HR 0.87; 95 % CI 0.53–1.44; $p = 0.597$). For OS, a slight and barely significant survival benefit in non-obese women revealed by a univariate log-rank test ($p = 0.047$; see Fig. 4c) was not confirmed by multivariate Cox regression (HR 1.23; 95 % CI 0.70–2.16; $p = 0.468$).

Discussion

Our data show that obesity constitutes an independent, adverse risk factor in patients with node-positive high-risk primary breast cancer. Women who were obese (BMI ≥ 30 kg/m^2) at the time of breast cancer diagnosis had a significantly shorter DFS and OS as compared to women who were non-obese (BMI < 30 kg/m^2) at the time of primary diagnosis. No differences in DFS or OS were found between overweight (BMI 25–29.9 kg/m^2) and underweight/normal-weight (BMI < 25 kg/m^2) patients. Subgroup analyses showed that the association of obesity with poor DFS and OS was significant for postmenopausal

Fig. 4 Kaplan–Meier plots according to BMI group (non-obese, obese) of disease-free survival in patients with hormone-receptor-negative (**a**) and hormone-receptor-positive (**b**) tumors, and of overall survival in patients with hormone-receptor-negative (**c**) and hormone-receptor-positive (**d**) tumor

patients, while no such association was found for pre-menopausal patients. Furthermore, a significant inverse relationship between obesity and outcome was found for patients with hormone-receptor-positive breast cancer, but not for patients with hormone-receptor-negative disease.

The association between obesity and breast cancer risk is well known, and two recent large meta-analyses have confirmed that obesity constitutes a risk factor for breast cancer recurrence and poor survival [13, 14]. Obese women with breast cancer are typically diagnosed late in life, have large primary tumors and a high number of lymph node metastases [15–17]. Thus, the advanced or potentially more aggressive disease of women with a high BMI at diagnosis might contribute to the worse prognosis found in obese breast cancer patients. We investigated whether obese patients had also more advanced tumors at the time of primary diagnosis in our pre-selected study sample of patients with high-risk node-positive disease (pT1–4, pN2–3, pM0). While we found no differences regarding grading, hormone receptor status or Her2 status, overweight and obese patients were diagnosed at an older age, had larger tumors and were more likely to be postmenopausal than underweight/normal-weight patients. However, our results showed that BMI significantly affects DFS and OS independently from other well-known prognostic tumor characteristics, in accordance

with several other studies that have demonstrated the prognostic role of BMI for recurrence and/or survival independently from histopathological tumor features [12, 18, 19].

To our knowledge, there are only two other studies that explicitly investigated the effect of obesity on DFS and OS in node-positive breast cancer patients based on data collected in randomized clinical trials. A retrospective analysis of patients enrolled in the randomized Phase-III BIG 02-98 trial reported that obesity was associated with poorer outcome independently from other prognostic factors [19]. In contrast, a recent pooled analysis of two randomized French trials found no significant influence of obesity on DFS or OS after adjusting for tumor characteristics [20]. Both studies differed from our study with regard to the number of positive lymph nodes of patients included; while the majority of patients in these two studies had only 1–3 positive lymph nodes, our study comprised only high-risk patients with more than 3 positive lymph nodes. Nevertheless, the reason for the lack of a significant negative effect of obesity on breast cancer prognosis in the French population remains unclear, and the authors could only speculate that local dietary habits and/or types and intensities of adjuvant chemotherapies might reduce the negative impact of obesity [20].

Similar to menopausal status, evidence for an effect of hormone receptor status on the association between obesity

and survival in breast cancer patients is equivocal. Some studies found that obesity was associated with poor survival independently from hormone receptor status [21, 22], while other studies reported that the association between obesity and inferior outcome was more pronounced for patients with hormone-receptor-positive breast cancer [17, 23].

Most recently, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) presented the results of a large study comprising 80,000 women enrolled in 70 clinical trials [24]. Quite surprisingly, obesity significantly increased the risk of breast cancer-related mortality in premenopausal women with estrogen-receptor-positive breast cancer compared to normal-weight patients, but had little effect on breast cancer-related mortality in postmenopausal women with estrogen-receptor-positive disease. No effect of obesity on breast cancer-related mortality in women with estrogen-receptor-negative disease was found.

Overall, the conflicting results regarding the effect of menopausal and hormone receptor status on the association between obesity and outcome in breast cancer patients, which might partly be due to differences with regard to patient cohorts and received treatments, show that currently the mechanisms underlying the link between obesity and prognosis are complex and far from being completely understood. Studies that found an association between obesity and outcome in premenopausal and/or hormone-receptor-negative breast cancer patients suggest that molecular mechanisms not related to sex hormone levels play an important role, at least in particular subgroups. Clearly, both more basic research on the molecular mechanisms and carefully designed clinical trials are needed to increase our understanding of the apparently complex link between obesity and breast cancer.

However, despite the limited knowledge regarding the mechanistic link, it seems clear that obesity plays a significant role for prognosis at least in some breast cancer patients. Thus, dietary and lifestyle interventions resulting in weight loss have been suggested to reduce recurrence rates in addition to providing secondary benefits [25]. Several studies have shown that interventions based on controlling dietary quality and/or physical activity patterns can be successful in reducing body weight of breast cancer patients [26–28]. Two large clinical trials, the Women's Intervention Nutrition Study (WINS) and women's healthy eating and living (WHEL) have investigated the effect of dietary interventions on disease recurrence in early stage breast cancer patients [29, 30]. A reduction in dietary fat and modest average weight loss was associated with a reduced recurrence of breast cancer in the WINS trial [29]. This result, however, was not confirmed in the WHEL trial, in which dietary intervention neither resulted in weight loss nor changed breast cancer prognosis in patients [30]. SUCCESS C [31], DIANA-5 [32] and ENERGY [33] are

three large ongoing randomized lifestyle intervention trials on breast cancer patients that assess the effect of an intervention aimed at increased physical activity combined with dietary counseling on breast cancer recurrence and survival. The results of these studies will hopefully shed light on the question of whether lifestyle interventions in breast cancer patients targeting body weight and physical activity can indeed influence recurrence and survival.

In conclusion, our study showed that obesity constitutes an independent, adverse prognostic factor in high-risk node-positive breast cancer patients, in particular for postmenopausal women and women with hormone-receptor-positive disease. Obese high-risk breast cancer patients might benefit from adhering to a healthy lifestyle aiming at body weight control as part of a comprehensive oncologic therapy.

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