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Body Mass Index, PAM50 Subtype, and Outcomes in Node-Positive Breast Cancer: CALGB 9741 (Alliance)

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Abstract

Background: Obesity at diagnosis is associated with poor prognosis in women with breast cancer, but few reports have been adjusted for treatment factors.

Methods: CALGB 9741 was a randomized trial of dose density and sequence of chemotherapy for node-positive breast cancer. All patients received doxorubicin, cyclophosphamide, and paclitaxel, dosed by actual body weight. Height and weight at diagnosis were abstracted from patient records, and the PAM50 assay was performed from archived specimens using the NanoString platform. Relationships between body mass index (BMI), PAM50, and recurrence-free and overall survival (RFS and OS) were evaluated using proportional hazards regression, adjusting for number of involved nodes, estrogen receptor (ER) status, tumor size, menopausal status, drug sequence, and dose density. All statistical tests were two-sided.

Results: Baseline height and weight were available for 1909 of 2005 enrolled patients; 1272 additionally had subtype determination by PAM50. Median baseline BMI was 27.4 kg/m^2. After 11 years of median follow-up, there were 619 RFS events and 543 deaths. Baseline BMI was a statistically significant predictor of RFS (adjusted hazard ratio [HR] for each five-unit increase in BMI = 1.08, 95% confidence interval [CI] = 1.02 to 1.14, $P = .01$) and OS (adjusted HR = 1.08, 95% CI = 1.01 to 1.14, $P = .02$) BMI and molecular phenotypes were independent prognostic factors for RFS, with no statistically significant interactions detected.

Conclusions: BMI at diagnosis was a statistically significant prognostic factor in a group of patients receiving optimally dosed chemotherapy. Additional research is needed to determine the impact of weight loss on breast cancer outcomes and to evaluate whether this impact is maintained across tumor subtypes.

Obesity is a well-established risk factor for poor prognosis in women with early-stage breast cancer (1–4). Several reviews and meta-analyses have summarized the many studies looking at the relationship between body weight at the time of breast cancer diagnosis and cancer outcomes in women with early-stage disease. For example, a recent meta-analysis of 82 reports

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on this topic reported a 34% increase in breast cancer–related mortality and a 41% increase in overall mortality in women who were obese at the time of breast cancer diagnosis as compared with women who were of normal weight (4).

Some controversy exists regarding the interaction between tumor hormone receptor status and the relationship between body weight and breast cancer prognosis. A recent report from the Early Breast Cancer Trialists Group evaluating the relationship between body mass index (BMI) at diagnosis and breast cancer mortality in women with early-stage breast cancer participating in adjuvant therapy trials demonstrated a 34% increase in breast cancer mortality in obese premenopausal women with hormone receptor–positive cancer, but did not show any relationship between body weight and outcomes in women with hormone receptor–negative cancers (5). In contrast, a meta-analysis of 21 studies found no evidence of interaction by hormone receptor status on the relationship between obesity and outcomes (6).

The mechanisms underlying the relationship between BMI and prognosis in early breast cancer are not fully understood. Some reports have suggested that part of this excess in breast cancer mortality in obese women may arise because of differences in tumor biology, with obese women being more likely to develop high-grade or hormone receptor–negative tumors (7,8). Other work has focused on the role of treatment factors in mediating the relationship between body weight and cancer outcomes, given that obese patients have often received less aggressive or dose-reduced therapy in the adjuvant setting (9,10). Finally, translational work has demonstrated that metabolic hormones and inflammatory mediators are linked to both obesity and breast cancer outcomes (11–14), suggesting putative pathways through which host factors could influence cancer growth and progression.

In order to overcome the adverse impact of obesity on outcomes in early breast cancer, a better understanding of the factors driving the relationship between body weight and breast cancer outcomes is needed. We evaluated the relationship between body mass index and rates of breast cancer recurrence and all-cause mortality in patients who participated in Cancer and Leukemia Group B (CALGB) 9741, an adjuvant treatment trial for women with breast cancer that required weight-based dosing for all participants, regardless of BMI (15). Additionally, we evaluated the relationship between BMI and distribution of tumor subtypes, in order to provide better insight into whether obese patients developed tumors that were biologically more aggressive. Finally, given the conflicting data regarding the interaction between tumor hormone receptor status and the relationship between body weight and breast cancer prognosis, we explored the relationships among tumor subtype, BMI, and cancer recurrence.

Methods

The patient cohort for this study was taken from the study population of C9741 (15), a randomized trial testing the impact of chemotherapy drug sequence and dose density upon the risk of cancer recurrence in women with lymph node–positive breast cancer. All patients in C9741 received treatment with cyclophosphamide, doxorubicin, and paclitaxel. The study used a two-by-two factorial design. The first factor was drug sequence (concurrent doxorubicin and cyclophosphamide followed by paclitaxel vs doxorubicin, followed by paclitaxel followed by cyclophosphamide), and the second factor was dose-density (treatment cycles every two weeks with growth factor support vs every three weeks). The study protocol mandated that all chemotherapy be dosed by actual body weight. The protocol suggested a five-year course of tamoxifen for all premenopausal women with estrogen receptor–positive breast cancer and for all postmenopausal women regardless of hormone receptor status. Eligibility criteria included the presence of at least one involved lymph node, absence of metastatic cancer, and diagnosis of breast cancer within the past 84 days.

The study was open to enrollment between September 1997 and March 1999. The CALGB, Eastern Cooperative Oncology Group, Southwest Oncology Group, and North Central Cancer Treatment Group participated in the study (CALGB is now part of the Alliance for Clinical Trials in Oncology). All participants signed an institutional review board–approved, protocol-specific informed consent document meeting all federal and institutional regulatory requirements.

Measures

Height and weight at the time of participant enrollment (after definitive surgery but before initiation of systemic therapy) were abstracted from patient study charts stored at the Alliance Statistics and Data Center. BMI was calculated according to the formula: $BMI = weight\ (kg)/height\ (m)^2$. BMI categories were defined according to the World Health Organization as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (BMI ≥ 30 kg/m^2).

Verification of chemotherapy dosing was performed to ensure that overweight and obese patients received adequate doses of protocol therapy. Assessment of chemotherapy dose delivery was based upon cycle 1 doxorubicin administration tested as a dichotomous variable, with adequate delivery defined as receipt of as at least 95% of the expected dose. Expected dose was calculated according to the body surface area reported by the study site at the time of patient enrollment.

PAM50 subtype was assessed using paraffin-embedded archived tumor tissue for all patients from whom tissue was available. RNA extraction from either block punches or macrodissected slides was performed at Washington University Clinical Laboratory Improvement Amendment (CLIA) molecular laboratories using an isolation kit and procedures provided by NanoString Technologies, Inc., and expression profiles were generated on a Research Use Only (RUO) nCounter Analysis System and RUO PAM50 probe set. Raw data (RCC files) that passed sample and quality metrics were provided in a blinded fashion to NanoString Technologies for normalization and analysis with a proprietary PAM50 algorithm. Gene expression profiles were categorized using a four-level classifier: Luminal A, Luminal B, Basal-like, and HER2-enriched, based upon Pearson's distance to centroids reestablished for the nCounter platform.

Statistical Analysis

Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Descriptive statistics were used to summarize baseline BMI. Comparisons between patient and tumor characteristics and BMI categories were tested using the Mann-Whitney test and Pearson chi-squared test for continuous and categorical variables, respectively. The primary endpoint was recurrence-free survival (RFS) under the STEEP system (16), defined as time from study entry until first recurrence, whether local or distant, or death without recurrence. Patients who were alive and recurrence free were censored at the date of last status verification. Contralateral breast cancers and second

primary non-breast cancers were not considered failures; participants continued to be followed for RFS. With 1909 patients and 552 RFS events anticipated, there was 90% power to observe a hazard ratio of 1.32 under a median split of BMI when using a two-sided alpha of 0.05 for testing. Overall survival (OS), defined as time from study entry until death because of any cause, was a secondary study endpoint. Distributions of RFS and OS were calculated using the Kaplan-Meier product limit method.

The relationship between BMI and RFS was first explored in a proportional hazards regression model using nonlinear cubic spline functions knotted at evenly spaced quintiles (see Supplementary Figure 1, available online), and linear and

Table 1. Patient characteristics by baseline body mass index

		BMI category				
	P*	Underweight (<18.5 kg/m²)	Normal 18.5–24.9 kg/m²	Overweight (25–29.9 kg/m²)	Obese (≥30 kg/m²)	Total
Characteristic		No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Study patients		22 (1.1)	623 (32.6)	628 (32.9)	636 (33.3)	1909 (100)
Study patients		22 (100)	623 (100)	628 (100)	636 (100)	1909 (100)
Drug sequence	.25					
Sequential		12 (54.5)	307 (49.3)	293 (46.7)	332 (52.2)	944 (49.4)
Concurrent		10 (45.5)	316 (50.7)	335 (53.3)	304 (47.8)	965 (50.6)
Dose density	.38					
3 weeks		9 (40.9)	328 (52.6)	307 (48.9)	311 (48.9)	955 (50.0)
2 weeks		13 (59.1)	295 (47.4)	321 (51.1)	325 (51.1)	954 (50.0)
Age, y	<.001†					
20–29		4 (18.2)	126 (20.2)	98 (15.6)	63 (9.9)	291 (15.2)
30–39		8 (36.4)	241 (38.7)	199 (31.7)	216 (34.0)	664 (34.8)
40–49		5 (22.7)	178 (28.6)	204 (32.5)	233 (36.6)	620 (32.5)
50–59		4 (18.2)	65 (10.4)	107 (17.0)	109 (17.1)	285 (14.9)
60–69		1 (4.5)	13 (2.1)	20 (3.3)	15 (2.4)	49 (2.6)
(Median)		(50)	(48)	(51)	(51)	(50)
Ethnicity	<.001‡					
White		20 (90.9)	540 (86.7)	517 (82.3)	494 (77.7)	1571 (82.3)
Hispanic		0 (0)	17 (2.7)	30 (4.8)	33 (5.2)	80 (4.2)
African Amer		2 (9.1)	34 (5.5)	71 (11.3)	98 (15.4)	205 (10.7)
Asian		0 (0)	20 (3.2)	6 (1.0)	2 (0.3)	28 (1.5)
Other		0 (0)	11 (1.8)	4 (0.6)	8 (1.3)	23 (1.2)
Not reported		0 (0)	1 (0.2)	0 (0)	1 (0.2)	2 (0.1)
Menopausal	<.001					
Pre		10 (45.5)	364 (58.4)	304 (48.4)	272 (42.8)	950 (49.8)
Post		12 (54.5)	259 (41.6)	324 (51.6)	364 (57.2)	959 (50.2)
Tumor size, cm	.004					
At most 2		6 (27.3)	288 (46.2)	240 (38.2)	226 (35.5)	760 (39.8)
>2 but ≤5		16 (72.7)	322 (51.7)	371 (59.1)	396 (62.3)	1105 (57.9)
Missing		0 (0)	13 (2.1)	17 (2.7)	14 (2.2)	44 (2.3)
No. positive nodes	.44					
1–3		13 (59.1)	394 (63.2)	369 (58.8)	364 (57.2)	1140 (59.7)
4–9		7 (31.8)	171 (27.4)	184 (29.3)	185 (29.1)	547 (28.7)
10+		2 (9.1)	53 (8.5)	68 (10.8)	82 (12.9)	205 (10.7)
Missing		0 (0)	5 (0.8)	7 (1.1)	5 (0.8)	17 (0.9)
ER status	.71					
Negative		8 (36.5)	216 (34.7)	204 (32.5)	211 (33.2)	639 (33.5)
Positive		14 (63.6)	400 (64.2)	412 (65.6)	410 (64.5)	1236 (64.7)
Missing		0 (0)	7 (1.1)	12 (1.9)	15 (2.4)	34 (1.8)
PgR status	.87					
Negative		11 (50.0)	255 (40.9)	260 (41.4)	260 (40.9)	786 (41.2)
Positive		10 (45.5)	357 (57.3)	352 (56.1)	361 (56.8)	1080 (56.6)
Missing		1 (4.5)	11 (1.8)	16 (2.5)	15 (2.4)	43 (2.3)
Tamoxifen use	.30					
Yes		16 (72.7)	429 (68.9)	464 (73.9)	438 (68.9)	1347 (70.6)
No		6 (27.3)	185 (29.7)	159 (25.3)	186 (29.2)	532 (27.9)
Missing		0 (0)	9 (1.4)	5 (0.8)	12 (1.9)	26 (1.4)

* P value is from comparison of stated variable and body mass index category using a Pearson chi-squared test. Unless otherwise stated, comparisons are by specified categories. BMI = body mass index; ER = estrogen receptor; PgR = progestin receptor.
† Age as a continuous variable.
‡ Comparison of white vs all other ethnicities.

nonlinear BMI components were assessed using Wald-type tests (17). Next, multivariable proportional hazards regression models (18) evaluated the adjusted hazard ratio of RFS (and OS) for a linear increase of pretreatment BMI when including study factors (sequence of chemotherapeutic regimen [sequential vs concurrent] and cycle length [q2-week vs q3-week]) as well as patient/tumor characteristics of documented importance in early-stage breast cancer: estrogen receptor (ER) status (negative vs positive), tumor size (square root transformation), menopausal status (pre vs post) and number of positive lymph nodes (square root transformation). PAM50-intrinsic subtypes were evaluated as a four-level factor. Interactions between BMI and PAM50 subtype and between BMI and ER were tested in the multivariable model of RFS described above. The assumption of proportional hazards was evaluated using the methods from Grambsch and Therneau (19).

Adjusted hazard ratios from multivariable models are reported with 95% confidence intervals and Wald-type *P* values. A *P* value of less than .05 was considered statistically significant. All statistical inferences were performed using SAS v9.2 (Cary, NC) or R v3.1.1(20).

Results

Two thousand five individuals were enrolled in C9741, 1972 of whom initiated protocol treatment (see Supplementary Figure 2, available online). Primary study results have been published previously by Citron et al. (15). In brief, patients randomly assigned to every-two-week therapy experienced a statistically significant improvement in recurrence-free survival and overall survival as compared with those randomly assigned to every-three-week therapy (HR = 0.74, 95% CI = 0.59 to 0.93, *P* = .01 and HR = 0.69, 95% CI = 0.50 to 0.93, *P* = .01 for RFS and OS, respectively). There was no difference in outcomes between patients randomly assigned to concurrent vs sequential therapy.

Baseline BMI was available for 1909 of 2005 patients. These patients comprise the study sample for the current analysis. Of these patients, 1272 had PAM50 subtyping results available and comprise the sample for the PAM50 subset analyses. Baseline characteristics of the 1909 patients for whom pretreatment BMI was available are presented in Table 1. Half of the participants were premenopausal, 64.7% had estrogen receptor–positive tumors, 59.7% had one to three involved nodes, 57.9% had tumors between 2 and 5 cm, and 70.6% took tamoxifen. Median BMI was 27.4 kg/m^2 (range 16.1–74.8); 1.1% of patients were underweight, 32.6% were normal weight, 32.9% were overweight, and 33.3% were obese.

Baseline BMI and Tumor and Host Characteristics

BMI was associated with tumor size (*P* = .004) and patients' race, age, and menopausal status at registration (all *P* < .001). Overweight and obese women were more likely to be nonwhite (20.0% vs 14.3%) and postmenopausal (54.4% vs 41.4%) and more likely to have tumors bigger than 2 cm (63.1% vs 52.4%) compared with normal and underweight women. There was no relationship between BMI and number of involved nodes. BMI was not associated with estrogen or progesterone receptor status.

In the subgroup with tissue available for the PAM50 assessment (n = 1272), there was a moderate difference in the distribution of subtypes by BMI category (*P* = .03) (Table 2). The proportions of tumors that were Basal-like and HER2-enriched were generally similar across weight groups. In contrast, although the overall frequency of Luminal tumors was similar across weight groups, the proportion of Luminal tumors that were Luminal B was greater in obese women (52.2%) relative to overweight and normal weight women (44.7% and 37.9%, respectively).

BMI and Chemotherapy Dose Delivery

Dosing information was available for 1786 patients. Almost all patients received more than 95% of expected dose delivery for the first cycle of doxorubicin protocol therapy, with only 1.9% of patients receiving reduced doses of doxorubicin for the first cycle of treatment. There was no difference between the proportion of patients who received reduced-dose therapy by BMI category, with 1% of normal weight, 2% of overweight, and 3% of obese individuals receiving reduced doses of therapy for the first treatment cycle (*P* = .22).

Baseline BMI and Cancer Outcomes

At a median follow up of 11 years (range = 2–13 years), there were 619 RFS events and 543 deaths among the 1909 patients for whom baseline BMI was available. The univariate relationship between baseline BMI category and RFS is shown in Figure 1. In univariate analysis with spline regression models, a linear relationship between BMI and RFS was statistically significant (*P* < .04), while nonlinear components of the model did not reach nominal statistical significance (all *P*s > .4) (Supplementary Figure 1, available online). This supported considering BMI as a linear term in the regression models. In multivariable analyses adjusted for number of involved lymph nodes, tumor size, estrogen receptor status, menopausal status of the patient, and treatment arm, baseline BMI was a statistically significant predictor of RFS (*P* = .01) (Table 3). In this multivariable model, a five-unit increase in BMI corresponded to an 8% increase in risk of an RFS event (adjusted HR = 1.08, 95% CI = 1.02 to 1.14, *P* = 0.01).

Figure 1 also shows OS by BMI category. In multivariable analyses adjusted for the variables detailed above (data not shown), baseline BMI was a predictor of OS, with a five-unit increase in BMI corresponding to an 8% increase in the risk of death

Table 2. Baseline body mass index and distribution of PAM50 subtypes*

	BMI category				
	Underweight (<18.5 kg/m^2)	Normal (18.5–24.9 kg/m^2)	Overweight (25–29.9 kg/m^2)	Obese (≥30 kg/m^2)	Total
Subtype	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
PAM substudy patients	17	409	409	437	1272
Basal-like	5 (29.4)	101 (24.7)	73 (17.8)	105 (24.0)	284 (22.3)
HER2-enriched	4 (23.5)	81 (19.8)	83 (20.3)	83 (19.0)	251 (19.7)
Luminal A	3 (17.6)	141 (34.5)	140 (34.2)	119 (27.2)	403 (31.7)
Luminal B	5 (29.4)	86 (21.0)	113 (27.6)	130 (29.7)	334 (26.3)

* BMI = body mass index; HER2 = human epidermal growth factor receptor 2.

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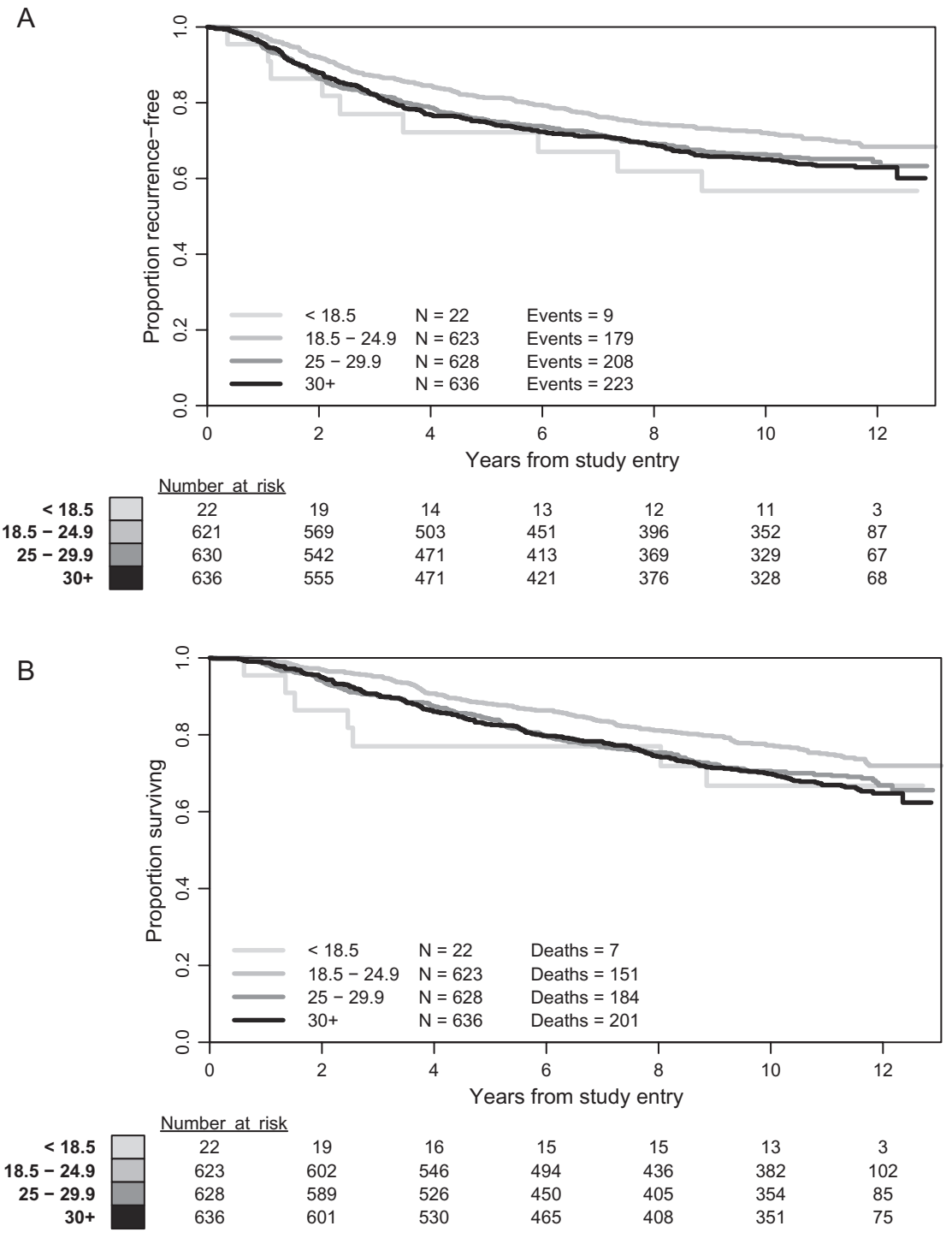

Figure 1. Recurrence-free **(A)** and overall **(B)** survival by body mass index. BMI = body mass index.

(adjusted HR = 1.08, 95% CI = 1.01 to 1.14, P = .02). There was no interaction between cycle length and the prognostic value of baseline BMI on RFS (P = .41) or on OS (P = .27).

BMI and Outcomes by Estrogen Receptor Status and PAM50

Multivariable models adjusted for known prognostic factors (as detailed above) did not demonstrate an interaction between estrogen receptor status and BMI (linearly modeled) on recurrence-free (P = .87) or overall survival (P = .53). For both estrogen receptor–positive and estrogen receptor–negative patients, there was an identical increase in the risk of both relapse and death with increasing BMI.

An exploratory analysis of the prognostic value of baseline BMI and PAM50 was performed using a multivariable model adjusting for the factors described above. In the subset with PAM50 data, BMI remained a statistically significant prognostic

Table 3. Observed effect of BMI on recurrence-free survival: results of multivariable proportional hazards model (n = 1845, 32% events)

Variable	HR comparison	HR (95% CI)	P*
BMI	5-unit increase	1.08 (1.02 to 1.14)	.01
No. nodes†	1: 10	0.44 (0.37 to 0.52)	<.001
Tumor size†	2 cm: 5 cm	0.72 (0.62 to 0.82)	<.001
Menopause	Post: pre	1.11 (0.94 to 1.31)	.22
ER status	Negative: positive	1.54 (1.31 to 1.82)	<.001
Sequence	Sequential: concurrent	1.05 (0.89 to 1.23)	.57
Dose density	q 3 wks: q 2 wks	1.21 (1.03 to 1.43)	.02

* P values are from a Wald-type test in the multivariable proportional hazards model. BMI = body mass index; CI = confidence interval; ER = estrogen receptor; HR = hazard ratio.
† A square root transformation was used in analyses as performed in Citron et al. (2003).

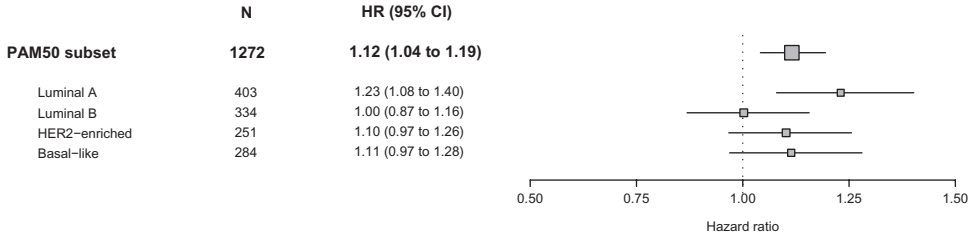

Figure 2. Recurrence-free survival by body mass index (BMI) in PAM50 subtypes. Hazard ratios are for a five-unit increase in BMI and displayed with 95% confidence intervals. The area of the **square** is proportional to the precision of the estimate. CI = confidence interval; HR = hazard ratio.

factor, with a five-unit increase in BMI resulting in a hazard ratio of 1.12 (95% CI = 1.04 to 1.19, *P* = .01) (Figure 2). In the multivariable model, the interaction test between the prognostic effects of BMI and intrinsic subtype did not reach statistical significance (3 df, *P* = .15). Within subgroups defined by PAM50, the unadjusted HR for each five-unit increase in BMI was highest at 1.23 (95% CI = 1.08 to 1.40) in Luminal A, lowest at 1.00 (95% CI = 0.87 to 1.16) in Luminal B, 1.10 (95% CI = 0.97 to 1.26) in HER2 enriched, and 1.11 (95% CI = 0.97 to 1.28) in the Basal-like subgroup.

Discussion

In a population of women with early-stage breast cancer treated with optimal doses of adjuvant chemotherapy, obesity was an independent prognostic factor for both recurrence-free and overall survival. Each five-unit increase in BMI (for example, increasing from a BMI of 22 mg/m^2, which is in the normal range, to a BMI of 27 kg/m^2, in the overweight range) was associated with an increase in the risk of cancer recurrence and death, or of death alone, of approximately 8%. Being underweight was also associated with poor prognosis, but these analyses were based on only a small number of patients; more work is needed to define the relationship between BMI and outcomes in underweight individuals. Obese patients were more likely to have larger tumors and to be postmenopausal, but the distributions of tumor grade and tumor hormone receptor status were similar across weight categories. In contrast, PAM50 subtypes were distributed differently in obese and nonobese individuals, with Luminal B tumors being more common and Luminal A tumors less common in obese individuals. Finally, exploratory analyses did not show an interaction between molecular subtype by PAM50 and the relationship between increased BMI and RFS, suggesting that obesity related to poor clinical outcome regardless of tumor subtype.

Our data demonstrating an increased risk of cancer recurrence and mortality in obese individuals with early-stage breast cancer are consistent with numerous studies reporting a relationship between BMI and cancer outcomes. However, in contrast to some reports, we found that increased BMI was associated with an increased risk of breast cancer recurrence and mortality regardless of hormone receptor status. In addition, exploratory analyses of the relationship between BMI and outcome in groups defined by PAM50 subtype suggested that BMI predicted outcomes in patients with Basal-like and HER2-enriched cancers, providing additional evidence that the relationship between body weight and breast cancer outcomes was not restricted to patients with hormone receptor–positive tumors.

Our study is one of the first to provide information regarding the relationship between biologic subtype and BMI in a large group of patients with early-stage breast cancer. Although the distribution of hormone receptor–positive and –negative cancers did not differ by weight category, our findings suggest that obese patients may have a different distribution of Luminal tumors as compared with leaner individuals. The higher proportion of Luminal B tumors could contribute to the poor outcomes seen in obese individuals, given that these cancers are associated with a higher risk of cancer recurrence as compared with Luminal A tumors. This finding needs to be replicated in other studies, but suggests that the biology of the tumors that obese women develop might account, at least in part, for the relationship seen between obesity and outcomes in breast cancer. It is not clear how this finding will influence the potential benefits of weight loss after cancer diagnosis in obese women with breast cancer; randomized trials are needed to evaluate the impact of purposeful weight loss on disease outcomes in women with early breast cancer overall and by biological subtype.

Our study has limitations that should be noted. Our sample size was relatively modest, and PAM50 data were only available for a subset of patients, limiting the power of our analyses; however, our dataset is larger than that included in any other report on the relationship between biologic subtype and BMI to date. These analyses should be viewed as hypothesis generating and require further validation. Our analyses were also retrospective and not preplanned. Although we adjusted these analyses for many known prognostic factors, it is possible that other factors we have not accounted for could influence the relationship between BMI and prognosis. We also lacked information regarding adherence to endocrine therapy,

given that the trial focused on the impact of chemotherapy on disease outcomes. Finally, our patient population was largely white, and thus it is not clear how these findings relate to minority populations, who are often disproportionally affected by obesity. Further evaluation of the relationship between obesity and breast cancer outcomes is needed in these populations.

In conclusion, we found an increased risk of breast cancer recurrence and death in overweight and obese individuals with newly diagnosed breast cancer taking part in an adjuvant clinical trial of anthracycline and taxane-based chemotherapy. Obesity was linked to differences in the distribution of breast cancer subtypes, with more aggressive Luminal B cancers observed to be more prevalent in obese individuals, potentially contributing to the poor outcomes seen in this population. Finally, there was no interaction between tumor subtype and the relationship between body weight and prognosis, suggesting that obesity was predictive of poor outcomes across biological subtypes. More work is needed to validate our findings regarding biologic differences between cancers developed by obese and nonobese individuals, to elucidate the biologic mechanisms by which obesity affects prognosis, and to determine whether weight loss after breast cancer diagnosis can alleviate the inferior prognosis experienced by obese individuals with breast cancer.

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Notes

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References

1. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. *Breast Cancer Res Treat*. 2010;123(3):627–635.
2. Chlebowski R, Aiello E, McTiernan A. Weight loss in breast cancer patient management. *J Clin Oncol*. 2002;20(4):1128–1143.
3. Goodwin P. Energy Balance and Cancer Prognosis: Breast Cancer. In: McTiernan A, ed. *Cancer Prevention and Management Through Exercise and Weight Control*. Boca Raton, FL: Taylor and Francis Group; 2006:405–435.
4. Chan DS, Vieira AR, Aune D, et al. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol*. 2014;25(10):1901–1914.
5. Pan H. Effect of obesity in premenopausal ER+ early breast cancer: EBCTCG data on 80,000 patients in 70 trials. Paper presented at: American Society of Clincial Oncology Annual Meeting 2014; Chicago, IL.
6. Niraula S, Ocana A, Ennis M, Goodwin PJ. Body size and breast cancer prognosis in relation to hormone receptor and menopausal status: a meta-analysis. *Breast Cancer Res Treat*. 2012;134(2):769–781.
7. Abdel-Maksoud MF, Risendal BC, Slattery ML, Giuliano AR, Baumgartner KB, Byers TE. Behavioral risk factors and their relationship to tumor characteristics in Hispanic and non-Hispanic white long-term breast cancer survivors. *Breast Cancer Res Treat*. 2012;131(1):169–176.
8. Stark A, Stahl MS, Kirchner HL, Krum S, Prichard J, Evans J. Body mass index at the time of diagnosis and the risk of advanced stages and poorly differentiated cancers of the breast: findings from a case-series study. *Int J Obes (Lond)*. 2010;34(9):1381–1386.
9. Griggs JJ, Mangu PB, Anderson H, et al. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2012;30(13):1553–1561.
10. Griggs JJ, Sorbero ME, Lyman GH. Undertreatment of obese women receiving breast cancer chemotherapy. *Arch Intern Med*. 2005;165(11):1267–1273.
11. Goodwin P, Ennis M, Pritchard K, Trudeau M. Fasting Insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J Clin Oncol*. 2002;20(1):42–51.
12. Goodwin P. Insulin in the adjuvant breast cancer setting: a novel therapeutic target for lifestyle and pharmacologic interventions? *J Clin Oncol*. 2008;26(6):833–834.
13. Duggan C, Irwin ML, Xiao L, et al. Associations of insulin resistance and adiponectin with mortality in women with breast cancer. *J Clin Oncol*. 2011;29(1):32–39.
14. Pierce BL, Ballard-Barbash R, Bernstein L, et al. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. *J Clin Oncol*. 2009;27(21):3437–3444.
15. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol*. 2003;21(8):1431–1439.
16. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol*. 2007;25(15):2127–2132.
17. Harrell FE. Regression modeling strategies: R package version 3.6-3. http://CRAN.R-project.org/package=rms. 2013; http://CRAN.R-project.org/package=rms.
18. Cox DR. Regression models and life-tables. *J R Stat Soc Ser B-Stat Methodol*. 1972;34(2):187.
19. Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81:515–526.
20. R core team. R: A language and environment for statistical computing. *R Foundation for Statistical Computing*, Vienna, Austria. http://www.R-project.org/. 2014.