Prognostic Value of Body Mass Index in Locally Advanced Breast Cancer

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Abstract

Purpose: The purpose of this retrospective study was to determine the association and prognostic value of body mass index (BMI) at the time of initial diagnosis in patients with locally advanced breast cancer (LABC). The analysis includes the subsets of inflammatory (IBC) and noninflammatory (non-IBC LABC) breast cancer.

Experimental Design: We identified 602 patients who had LABC treated on prospective clinical trials. BMI was divided into three groups: (*a*) ≤24.9 (normal/underweight), (*b*) 25.0 to 29.9 (overweight), and (*c*) ≥30 (obese). Kaplan-Meier product limit method was used to estimate survival outcomes. Cox proportional hazards were used to determine associations between survival and BMI and to test for an interaction between BMI and breast cancer type.

Results: Eighty-two percent had non-IBC LABC and 18% had IBC. Obese patients tended to have a higher incidence of IBC compared with overweight and normal/underweight groups ($P = 0.01$). Median follow up was 6 years for all patients. Median overall survival (OS) and recurrence-free survival (RFS) were 8.8 and 5.9 years, respectively. Patients with LABC who were obese or overweight had a significantly worse OS and RFS ($P = 0.001$) and a higher incidence of visceral recurrence compared with normal/underweight patients. In a multivariable model, BMI remained significantly associated with both OS and RFS for the entire cohort. The interactions between BMI and LABC subsets and between BMI and menopausal status were not statistically significant.

Conclusion: Patients with LABC and high BMI have a worse prognosis. Evaluation of the biological factors associated with this observation can provide tools for additional therapeutic interventions.

Locally advanced breast cancer (LABC) is an important public health problem, representing ~5% of newly diagnosed breast cancers among women enrolled in periodic screening programs and up to 50% of women in medically underserved regions of the United States and many developing countries (1).[4] Inflammatory breast cancer (IBC), an aggressive and highly lethal form of breast cancer, represents a distinct subset of LABC that constitutes ~1% to 6% of breast cancers diagnosed in the United States (2).

A number of factors including tumor size, number of involved lymph nodes, estrogen receptor status, nuclear grade, and human epidermal growth factor receptor-2 status are known to influence prognosis of breast cancer (3, 4). A growing body of evidence suggests that body weight is also strongly associated with increasing risk of developing breast cancer (5, 6). Furthermore, patients with higher body mass index (BMI) have been found to have worse outcome (7, 8) and a higher risk of recurrence regardless of age or menopausal status (9, 10). In addition, women with higher fat content tend to have larger tumors and more involved lymph nodes at presentation (11, 12).

Earlier studies have shown that high BMI was associated not only with a higher risk of developing IBC (13) but also with shorter survival (14). At the University of Texas M. D. Anderson Cancer Center, we have treated patients with locally advanced breast cancer in clinical trials using similar multimodality therapies (15, 16). The uniformity of treatments and follow-up procedures gives us the opportunity to evaluate the effect of biological factors with minimal confounding bias of other variables. We therefore decided to perform a retrospective study to determine the association and prognostic value of BMI in LABC and to determine if the effect of BMI was different between the non-IBC LABC and IBC subgroups.

Patients and Methods

Patient population. Women with breast cancer treated according to clinical protocols, conducted in the Breast Medical Oncology Department

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[4] https://web.facs.org/ncdbr/help.compare6/ver6.site.stage.2001.htm

Table 1. Patient characteristics by BMI group

	Obese, *n* (%)	Overweight, *n* (%)	Normal or underweight	*P*
n	204	194	208	
Type				
Non-IBC LABC	154 (75.5)	161 (83.0)	180 (86.5)	
IBC	50 (24.5)	33 (17.0)	28 (13.5)	0.01
Age				
Minimum	28 (—)	23 (—)	23 (—)	
Median	52 (—)	48 (—)	46 (—)	
Maximum	78 (—)	78 (—)	76 (—)	0.001
Menopause				
Post	109 (53.4)	80 (41.2)	83 (39.9)	
Pre	72 (35.3)	93 (47.9)	104 (50.0)	
Unknown	23 (11.3)	21 (10.8)	21 (10.1)	0.004
T stage				
T_0	5 (2.5)	1 (0.5)	2 (1.0)	
T_1	1 (0.5)	5 (2.6)	7 (3.4)	
T_2	15 (7.4)	16 (8.2)	27 (13.0)	
T_3	34 (16.7)	33 (17.0)	54 (26.0)	
T_4	133 (65.2)	133 (68.6)	112 (53.8)	0.01
Unknown	16 (7.8)	6 (3.1)	6 (2.9)	
N stage				
N_0	16 (7.8)	19 (9.8)	21 (10.1)	
N_1	60 (29.4)	77 (39.7)	73 (35.1)	
N_2	113 (55.4)	68 (35.1)	90 (43.3)	
N_3	13 (6.4)	30 (15.5)	23 (11.1)	
Unknown	2 (1.0)	0 (0.0)	1 (0.5)	0.002
HR				
Negative	63 (30.9)	49 (25.3)	50 (24.0)	
Positive	81 (39.7)	73 (37.6)	84 (40.4)	
Unknown	60 (29.4)	72 (37.1)	74 (35.6)	0.55
Grade				
1	4 (2.0)	5 (2.6)	3 (1.4)	
2	38 (18.6)	41 (21.1)	63 (30.3)	
3	118 (57.8)	99 (51.0)	92 (44.2)	
Unknown	44 (21.6)	49 (25.3)	50 (24.0)	0.03
Chemotherapy type				
A	146 (71.6)	156 (80.4)	177 (85.1)	
A + T	58 (28.4)	38 (19.6)	31 (14.9)	0.003
X-ray therapy				
Adjuvant	159 (77.9)	154 (79.4)	166 (79.8)	
Neoadjuvant	9 (4.4)	8 (4.1)	11 (5.3)	
None	24 (11.8)	14 (7.2)	20 (9.6)	
Unknown	12 (5.9)	18 (9.3)	11 (5.3)	0.67
Surgery type				
BCS	27 (13.2)	20 (10.3)	20 (9.6)	
Mastectomy	154 (75.5)	156 (80.4)	174 (83.7)	
None	13 (6.4)	13 (6.7)	14 (6.7)	
Unknown	10 (4.9)	5 (2.6)	0 (0.0)	0.73
Pathologic complete response				
No	163 (79.9)	156 (80.4)	165 (79.3)	
Yes	18 (8.8)	20 (10.3)	28 (13.5)	
Unknown	23 (11.3)	18 (9.3)	15 (7.2)	0.38

Abbreviations: HR, hazard ratio; BCS, breast-conserving surgery; A, Adriamycin; T, taxanes.

of the M. D. Anderson Cancer Center between 1974 and 2000, composed the cohort for this Institutional Review Board–approved retrospective study. All treatment protocols studied the role of an anthracycline-based primary systemic treatment, details of which have already been described (15, 16). Patients included in the analysis were restricted to those with nonmetastatic inflammatory (IBC) and noninflammatory locally advanced breast cancers (non-IBC LABC) that were classified as stage III according to American Joint Committee on Cancer criteria (17). IBC was defined according to consistent institutional clinical diagnostic criteria that included rapidly developing (<3 months) signs and symptoms of diffuse erythema, peau d'orange, and increasing size of the breast with or without evidence of extensive dermal lymphatic invasion on core biopsy specimens. Variables recorded included height and weight at time of initial diagnoses, tumor and patient characteristics, treatment administered, and site of recurrence.

Statistical analysis. BMI was calculated by dividing weight in kilograms by the square of height in meters. BMI categories were defined following the Centers of Disease Control and Prevention[5] classification: (*a*) BMI <18.5 kg/m^2 was categorized as underweight;

[5] http://www.cdc.gov/nccdphp/dnpa/obesity/trend/index.htm

Table 2. Cumulative incidence of visceral recurrence by breast cancer type and BMI group

	Non-IBC LABC, *n* = 495		IBC, *n* = 111	
	5 y (%)	10 y (%)	5 y (%)	10 y (%)
Obese	30.7	33.4	19.9	29.9
Overweight	29.2	33.4	50.9	50.9
Normal/under weight	19.5	20.9	17.9	17.9

(*b*) BMI 18.5 to 24.9 kg/m^2 was categorized as normal weight; (*c*) BMI 25.0 to 29.9 kg/m^2 was categorized as overweight; (*d*) BMI ≥30 kg/m^2 was categorized as obese. For our analysis, patients in the underweight and normal weight BMI categories were combined into one group.

Patient characteristics were tabulated and compared between BMI groups with the χ^2 test. Overall survival (OS) was calculated from the start of treatment to the date of death from any cause or last follow-up. Recurrence-free survival (RFS) was calculated from the start of treatment to the date of disease recurrence or last follow-up. Patients who died before experiencing a disease recurrence were considered censored at their date of death. Median follow-up was calculated as the median observation time among all patients and also as the median observation time among patients still alive at their last follow-up. Survival distributions were estimated with the Kaplan-Meier product limit method and compared between groups with the log-rank statistic. Univariate Cox proportional hazards models were fit to determine associations between survival outcomes and continuous variables. Multivariable Cox proportional hazards models were fit to determine the association between BMI and survival outcomes after adjustment for other patient characteristics and to test for an interaction between BMI and breast cancer type (IBC and non-IBC LABC). Each multivariable model included terms for breast cancer type, BMI, and year of diagnosis. Additional variables were considered for inclusion based on the likelihood ratio test. The proportional hazards assumption was assessed visually with plots of the model residuals. We estimated the cumulative incidence of visceral recurrence using the method of Gooley et al. (18). Death before recurrence and recurrences at other sites were considered competing risks. $P < 0.05$ was considered statistically significant.

Results

Study population. Nine hundred nine patients with stage III LABC (IBC and non-IBC LABC) were identified, of which 606 had baseline height and weight data available for BMI calculation and were included in the analysis. Table 1 shows the tabulation of patient characteristics by BMI group. Five hundred ninety-five (82%) patients had non-IBC LABC and 111 (18%) patients had IBC. According to BMI, 208 (34%) patients were normal/underweight, 194 (32%) patients were overweight, and 204 (34%) patients were obese. Median age of presentation was higher for obese patients (52 years) than normal/underweight (46 years) and overweight (48 years) patients. Obese patients were observed to have a higher incidence of IBC than overweight and normal/underweight

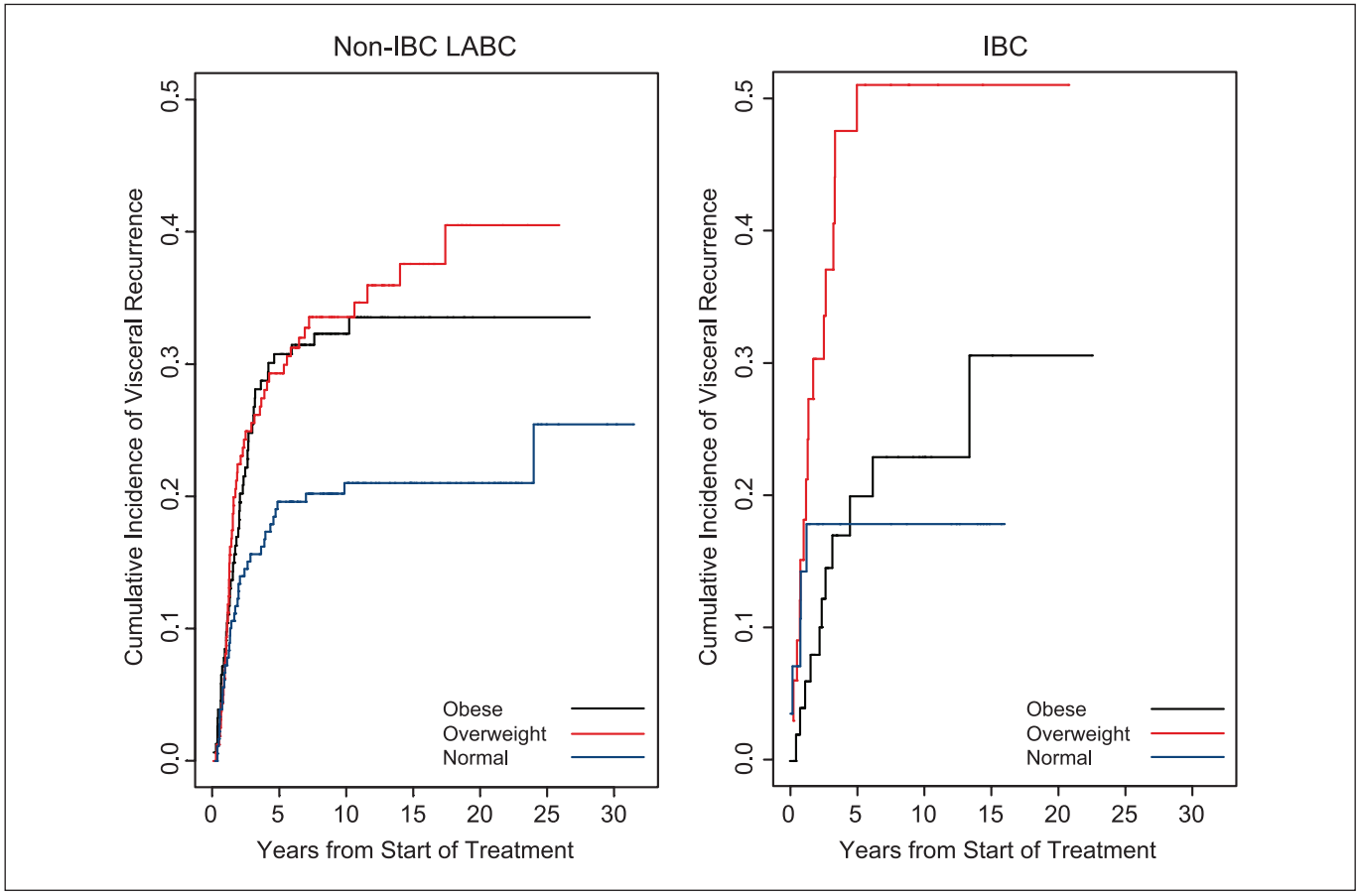

Fig. 1. Cumulative incidence of visceral recurrence by breast cancer type (non-IBC LABC and IBC) and BMI.

Table 3. Univariate analyses of OS

	n	Events, *n*	Median	5 y [% (95% CI)]	10 y [% (95% CI)]	*P*
All	606	341	8.6	60.3 (56.5-64.4)	47.3 (43.2-51.7)	
BMI						
Obese	204	118	7.1	56.8 (50.2-64.2)	42.7 (35.9-50.8)	
Overweight	194	120	6.0	56.3 (49.7-63.8)	41.8 (35.1-49.9)	
Normal	208	103	12.7	67.4 (61.3-74.1)	56.5 (49.9-64)	0.001
Type						
Non-IBC LABC	495	279	9.6	62.4 (58.3-66.8)	48.4 (44-53.1)	
IBC	111	62	4.6	49.7 (40.7-60.8)	41.4 (32.5-52.8)	0.08
Non-IBC LABC						
Obese	154	91	7.5	58.6 (51.3-67)	42.4 (34.7-51.7)	
Overweight	161	99	7.3	58.3 (51.2-66.5)	44.1 (36.7-53)	
Normal/underweight	180	89	12.8	69.3 (62.8-76.4)	57.3 (50.2-65.4)	0.003
IBC						
Obese	50	27	4.3	49.3 (36.1-67.4)	43.7 (30.6-62.3)	
Overweight	33	21	4.4	45.3 (30.5-67.2)	29.1 (16.1-52.5)	
Normal/underweight	28	14	12.2	55.1 (39-77.9)	50.9 (34.8-74.4)	0.45

patients (P = 0.01) and tended to be postmenopausal more frequently at the time of presentation. In addition, overweight and obese patients tended to present with tumors of higher T stage, higher nodal involvement, and higher grade compared with patients who were normal/underweight at baseline presentation.

Recurrence and survival outcomes. Median follow-up among all patients was 6.0 years (range, 0.1-30.6 years) and median follow-up among patients still alive at their last follow-up was 9.9 years (range, 1.5-30.6 years). Of the 606 patients included in this analyses, 341 (56%) patients have died and 325 (54%) patients have experienced a recurrence. Estimates of the cumulative incidence of visceral recurrence by breast cancer type and BMI group are shown in Table 2, and plots of the cumulative incidence curves are shown in Fig. 1. Obese and overweight patients had higher rates of visceral recurrence compared with normal/underweight patients.

Tables 3 and 4 list the OS and RFS estimates, respectively. Median OS and RFS for the entire cohort were 8.6 and 5.8 years, respectively. OS and RFS were significantly worse for obese and overweight patients compared with normal/underweight (P = 0.001). Five-year OS and RFS for IBC patients were 49.7% [95% confidence interval (95% CI), 40.7-60.8%] and 39.9% (95% CI, 31.4-50.7%), respectively. Five-year OS and RFS for non-IBC LABC were 62.4% (95% CI, 58.3-66.8%) and 54.8% (95% CI, 50.5-59.4%), respectively. In each subgroup, OS and RFS among patients classified as obese or overweight were worse compared with patients classified as normal/underweight (Figs. 2 and 3).

Table 5 shows the results of the multivariable models for OS and RFS. T stage, tumor size, and surgery type were not considered for inclusion in the models because they were collinear with breast cancer type. Nuclear grade, pathologic stage, and hormone receptor status were not considered for inclusion in the model because of the large amount of missing data associated with these variables. The interaction between BMI and breast cancer type was not statistically significant (likelihood ratio test: P = 0.22 for OS, P = 0.27 for RFS). The interaction between BMI and menopausal status was not statistically significant for both OS (P = 0.95, likelihood ratio test) and RFS (P = 0.71, likelihood ratio test). After adjustment for year of diagnosis, menopausal status, number of lymph nodes removed, number of positive lymph nodes, presence or absence of taxanes in the treatment regimen, and pathologic complete response, RFS was worse for IBC than non-IBC LABC (hazard ratio, 1.35; 95% CI, 0.99-1.86; P = 0.06). However, OS

Table 4. Univariate analyses of RFS

	n	Events, *n*	Median	5 y [% (95% CI)]	10 y [% (95% CI)]	*P*
All	606	325	5.8	52.1 (48.3-56.4)	46.0 (42-50.3)	
BMI						
Obese	204	114	4.5	49.2 (42.7-56.7)	42.0 (35.3-49.9)	
Overweight	194	117	3.5	45.2 (38.6-52.9)	40.9 (34.4-48.7)	
Normal	208	94	23.3	61.5 (55.1-68.6)	54.6 (47.9-62.2)	0.001
Type						
Non-IBC LABC	495	258	8.1	54.8 (50.5-59.4)	47.6 (43.2-52.5)	
IBC	111	67	2.7	39.9 (31.4-50.7)	38.7 (30.2-49.5)	0.01
Non-IBC LABC						
Obese	154	84	5.4	51.7 (44.3-60.3)	43.3 (35.7-52.5)	
Overweight	161	93	4.3	49.3 (42-57.7)	44.2 (37-52.8)	
Normal/underweight	180	81	23.3	62.4 (55.7-70)	54.5 (47.4-62.8)	0.009
IBC						
Obese	50	30	2.8	41.3 (29.1-58.5)	38.3 (26.2-55.9)	
Overweight	33	24	1.9	24.4 (13-45.7)	24.4 (13-45.7)	
Normal/underweight	28	13	14.6	56.9 (41.2-78.7)	56.9 (41.2-78.7)	0.23

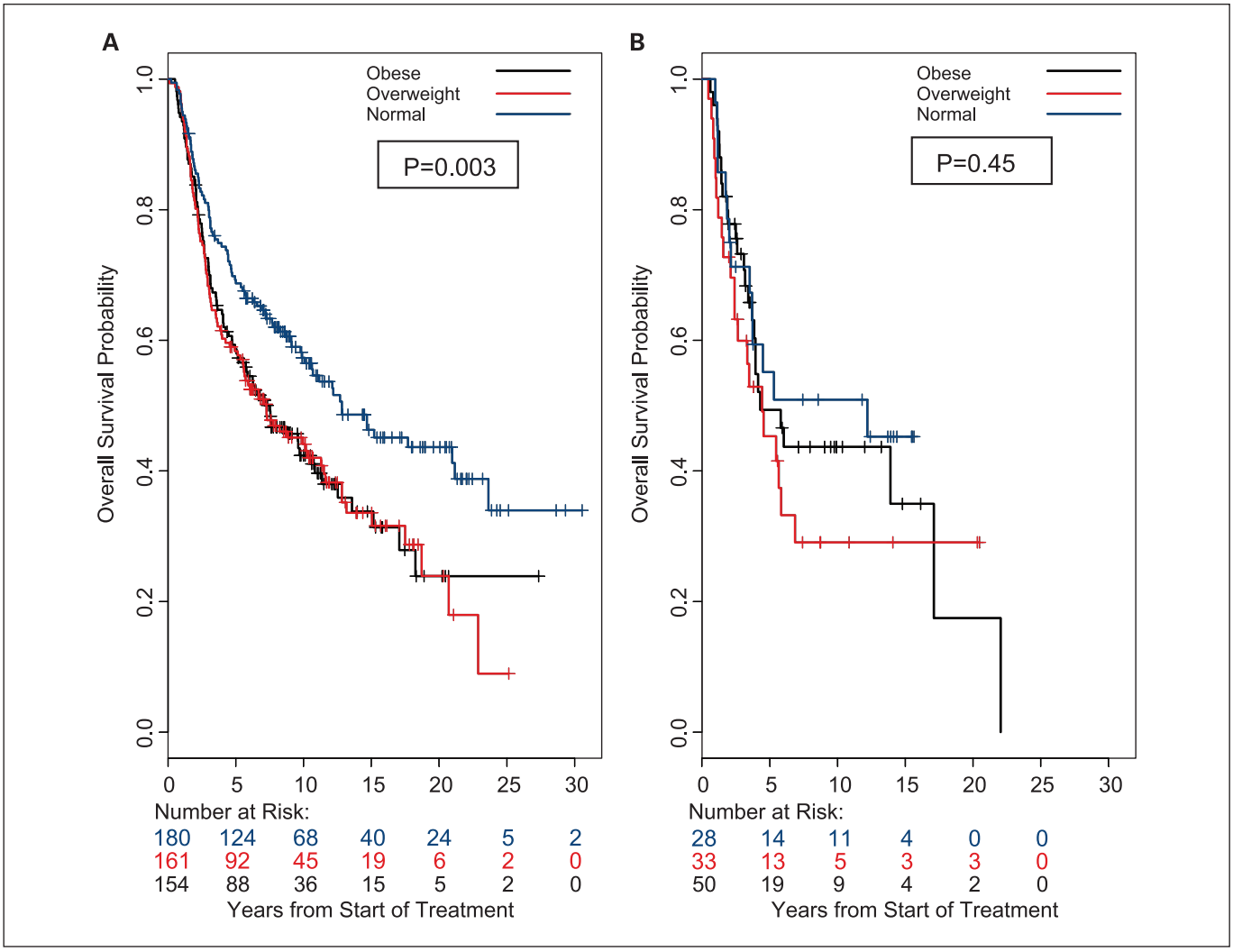

Fig. 2. OS by breast cancer type and BMI group. *A,* differences in survival in patients with non-IBC locally advanced breast cancer were statistically significant. *B,* differences in survival across the three BMI groups among patients with inflammatory breast cancer were not statistically significant.

was not statistically different between the two types. BMI remained significantly associated with both OS and RFS in the multivariable model, with obese and overweight patients doing worse than normal/underweight patients.

Discussion

The purpose of this study was to determine the association and prognostic value of BMI, determined at diagnoses, in patients with LABC, including both subsets (IBC and non-IBC LABC). More than 60% of American adults are either overweight or obese, a phenomenon also observed in our cohort wherein nearly 66% of all patients were overweight or obese.[6] In our cohort, obese LABC patients tended to have a higher incidence of IBC compared with overweight and normal/underweight groups. Furthermore, patients with LABC who were obese and overweight had a statistically significant worse OS and RFS, with a higher incidence of visceral recurrence. Results were similar in the non-IBC LABC and IBC subgroups.

A substantial body of evidence exists that has linked obesity with an increased risk of developing breast cancer (5, 6). The association between obesity and breast cancer prognosis has been far less clear. In a systematic review, Chlebowski et al. (8) showed that numerous investigations, collectively incorporating >29,000 women with invasive breast cancer, revealed a statistically significant increased risk of disease recurrence and mortality in obese women compared with lean women, with hazard ratios ranging from 1.3 to well over 2. Berclaz et al. (19) subsequently confirmed these results on a cohort of 6,792 women with early-stage breast cancer treated on various clinical trials conducted by the International Breast Cancer Study Group, albeit with more modest hazard ratios. In sharp contrast, in an analysis of 3,385 women with node-negative, estrogen receptor–positive breast cancer treated on the National Surgical Adjuvant Breast and Bowel Project B-14 (20) trial, obesity was not associated with increased risk of recurrence or increased breast cancer mortality. One explanation for this is the fact that the cohort studied in the National Surgical Adjuvant Breast and Bowel Project B-14 trial

[6] http://www.cdc.gov/nccdphp/dnpa/obesity/trend/index.htm

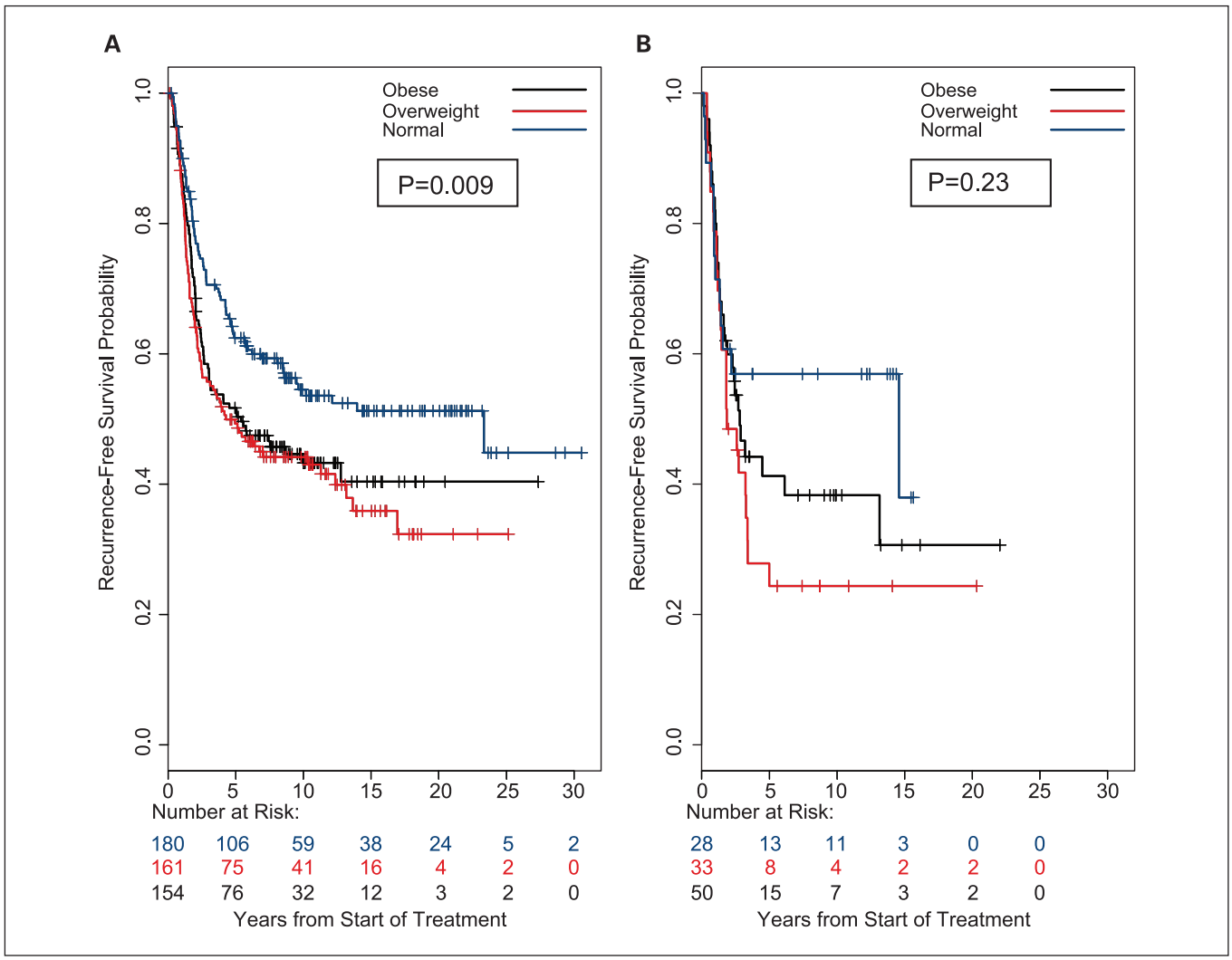

Fig. 3. RFS by breast cancer type and BMI Group. *A,* differences in survival in patients with non-IBC locally advanced breast cancer were statistically significant. *B,* differences in survival across the three BMI groups among patients with inflammatory breast cancer were not statistically significant.

included women with an already good prognostic outcome based on stage and estrogen receptor status. In our study, we limited our analysis to a cohort of women with LABC, a cohort considered to have poor long-term outcome, that were all treated in a similar multidisciplinary fashion and received similar systemic and local treatments. The results clearly give unique insight into the prognostic value of BMI in this cohort, with obese and overweight women presenting with tumors with adverse prognostic factors (i.e., higher T stage, nodal involvement, and grade) having associated increased risk of disease recurrence and increased mortality. This difference was also observed in the non-IBC LABC and IBC subgroups, although the differences were not as striking

Table 5. Multivariable model results

	OS		RFS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
BC type (IBC vs non-IBC LABC)	0.93 (0.62-1.38)	0.70	1.35 (0.99-1.86)	0.06
Overweight vs normal weight	1.64 (1.22-2.21)	0.001	1.55 (1.16-2.09)	0.004
Obese vs normal weight	1.40 (1.03-1.91)	0.03	1.42 (1.05-1.92)	0.02
Year of diagnosis (continuous)	0.97 (0.94-0.99)	0.005	0.97 (0.94-0.99)	0.005
No. positive lymph nodes (continuous)	1.09 (1.07-1.11)	<0.0001	1.08 (1.06-1.11)	<0.0001
No. lymph nodes removed (continuous)	0.96 (0.93-0.98)	<0.0001	0.95 (0.93-0.97)	<0.0001
Menopausal status (pre vs post)	0.59 (0.39-0.88)	0.01	—	—
Pathologic complete response (yes vs no)	—	—	0.56 (0.34-0.95)	0.03
Age (continuous)	0.99 (0.97-1.01)	0.22	1.00 (0.99-1.01)	0.70
Chemotherapy (A + T vs A)	1.36 (0.73-2.52)	0.33	0.92 (0.60-1.41)	0.70

in the IBC subgroup. This may be explained by both the small number of IBC patients included in the analysis (most of them with high BMI), reflecting the relative rarity of the disease, and the more aggressive biology of IBC compared with non-IBC LABC, which may have somewhat offset the prognostic effect of BMI. Visually, it is not obvious that an interaction between BMI and LABC subgroups exists; furthermore, in the multivariable model, the interaction term was not statistically significant. This may indicate a similar prognostic effect of BMI between the two subgroups.

The lack of interaction between BMI and menopausal status that was observed in our study may have been due to the fact the cohort studied already had a poor prognostic outcome due to their advanced stage and aggressive biological features of high nodal stage and nuclear grade. However, there is a growing body of evidence (9, 10) indicating that high BMI is associated with poor clinical outcome regardless of the menopausal status, a phenomenon observed in our study. A mechanism traditionally used to explain the role of high BMI in increased recurrence risk in postmenopausal women is the excessive production of estrogens through peripheral aromatization of adrenal steroids in adipose tissue (21). In premenopausal women, the mechanism is less clear, with factors such as hyperinsulinemia and hyperandrogenism thought to be potential mediators of the adverse prognostic effect of high BMI (22, 23). This, in part, as suggested by Ross et al. (24), may be mediated through increased levels of leptin, a neurocendocrine hormone that is produced predominantly in adipose tissue (25) and is a biomarker of obesity (26) that promotes tumor growth, invasion, and angiogenesis, thereby promoting a more aggressive tumor. A recent study by Goodwin et al. (27), evaluating the prognostic effect of leptin in a cohort of 471 women with early-stage breast cancer, showed that although elevated levels of leptin were associated with more advanced tumor stage, they did not predict for outcome. This may have been, in part, due to the small sample size studied and the fact that the majority of patients had node-negative and estrogen receptor–positive disease, factors known to predict for favorable long-term outcome. As a follow-up to our study, we are currently prospectively collecting leptin levels in patients with LABC (including IBC), with preliminary analysis of the data indicating higher baseline levels in patients with newly diagnosed IBC, although no prognostic information is yet available.

Once again, the strengths of this study lie in the fact that the cohort of patients included in the analysis were restricted to those enrolled in clinical trials conducted in a single institute. This allowed for a more homogenous patient population with respect to disease stage, specifically when considering patients with IBC where protocols mandate consistent diagnostic criteria, and treatment, where all patients received anthracycline-based chemotherapy. In addition, ''capping'' of body surface area used for calculation of chemotherapy doses in patients with higher BMI would result in under-dosing of chemotherapy, resulting in suboptimal treatment results and poorer outcomes. In our institution, body surface area was always calculated on actual body weight, without capping, and full doses of chemotherapy were administered both on and off clinical trials.

As with any study, our study had certain limitations. First, we were unable to assess changes in BMI longitudinally during and following treatment, a factor that has been shown in some trials to be of prognostic value (8, 28). However, because our study cohort was restricted to patients with LABC, where events are seen relatively early on, we hypothesize that the strongest prognostic effect of BMI would be at diagnoses of disease. Regardless, prospective studies designed to assess changes in BMI following disease diagnoses would be important to confirm this additional observation. Second, we lacked information on dietary habits following disease diagnoses. This would be particularly important because recent results of a large prospective trial of >2,000 postmenopausal women with primary breast cancer revealed an association between low dietary fat intake and reduced risk of disease recurrence (hazard ratio, 0.76; 95% CI, 0.60-0.98; $P = 0.034$; ref. 29). Finally, due to the retrospective nature of the study and the fact that we included patients from trials conducted in the 1970s and 1980s, a large amount of data were missing pertaining to the hormone receptor status and grade, factors known to be important markers of prognosis.

In conclusion, this large retrospective study including patients with more aggressive breast cancer shows a clear prognostic value of high BMI at the time of initial diagnoses. These results indicate the need for a systematic prospective evaluation of endocrinologic and immune-related factors in these patients. Furthermore, they highlight the need for dietary interventions as part of a multidisciplinary approach to the disease.

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