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The impact of obesity on receipt of adjuvant chemotherapy for breast cancer in the National Comprehensive Cancer Network (NCCN) centers

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Abstract

Disparities in the receipt of adjuvant chemotherapy for early stage breast cancer is an important factor influencing mortality. We investigated whether greater body mass index (BMI) decreases receipt of adjuvant chemotherapy among women with operable breast cancer. In the NCCN breast cancer outcomes database, we identified women age ≤70 with newly diagnosed stage I, II or III breast cancer between 1997 and 2007, for whom use of adjuvant chemotherapy was classified as either standard-of-care or discretionary based on their clinical characteristics. Body mass index was assessed in categories (<18.5 kg/m^2 [underweight], 18.5 to <25 kg/m^2 [normal], 25 to <30 kg/m^2 [overweight], 30 to 39kg/m^2 [obese], ≥40 kg/m^2 [extreme obese]). Multivariable logistic regression analysis was used to examine the association between BMI and receipt of chemotherapy in each classification group. 9,527 women were eligible for the study; 40% normal weight or less; 31% overweight; 24% obese; and 5% extremely obese. In multivariable analysis, there was no significant association between BMI and receipt of chemotherapy in either classification group. Among women for whom chemotherapy would be considered standard-of-care, older age (p<.001), comorbidity (p<.001), and non-Hispanic black ethnicity (p=.002) were associated with a lower likelihood of receipt of chemotherapy; however, the effect of ethnicity was not mediated by obesity. Among women treated for operable breast cancer in the NCCN centers, BMI had no impact on receipt of adjuvant chemotherapy and did explain the lower likelihood of chemotherapy among non-Hispanic black patients. Further investigation is needed into other factors that contribute to patient disparities in the receipt of chemotherapy in major academic centers.

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Keywords

Obesity; Breast Neoplasms; Chemotherapy; Adjuvant; Standard of Care; Healthcare Disparities

INTRODUCTION

The Early Breast Cancer Trialists's Collaborative Group (EBCTCG) overview of randomized trials in early stage breast cancer demonstrated that adjuvant polychemotherapy reduces risk of recurrence and improves survival [1]. Recent studies exploring patient-related factors that contribute to disparities in breast cancer survival have found that older age, black race and low socioeconomic status are associated with lower rates of receipt of adjuvant chemotherapy [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12]. While insurance status, decreased access to subspecialty care and geographical location have been shown to mediate some of the ethnic differences in receipt of appropriate breast cancer care, [9], [13], [14] the identification of additional patient-related factors that predict for the receipt of adjuvant chemotherapy could provide opportunities for interventions aimed towards improving breast cancer outcomes.

The rate of obesity has increased exponentially over the past decade with 64% of women in the United States estimated to be overweight or obese [15]. Several studies have documented a tendency for treating physicians to intentionally prescribe lower doses of adjuvant chemotherapy for obese patients, presumably because of concerns about drug metabolism or patient tolerance of side effects [16], [17], [18], [19]. Less is known about whether obesity affects the decision to use adjuvant chemotherapy. One small study of women treated for breast cancer in a network of HMOs found no association between obesity and receipt of chemotherapy, but larger confirmatory studies in other populations have not been performed [20]. Since higher rates of obesity are observed among lower socioeconomic and racial and ethnic minorities compared with more affluent and white populations[15],[21], [22, 23], it is possible that increased body weight may influence some of the ethnic differences in the receipt of adjuvant therapy.

Using the National Comprehensive Cancer Network (NCCN) Breast Cancer Outcomes database, which provides extensive clinical detail, we investigated the impact of BMI on receipt of chemotherapy in an ethnically diverse multi-institutional cohort of patients with stages I–III breast cancer. Furthermore, we examined whether BMI modifies ethnicity related disparities in receipt of adjuvant chemotherapy. To perform the analysis, we examined receipt of chemotherapy among patients for whom treatment would be considered standard-of-care as well those for whom treatment would be considered discretionary, hypothesizing that obesity would have a greater impact on influencing discretionary use of chemotherapy.

METHODS

Patient Selection

The study cohort consisted of women with newly diagnosed American Joint Committee on Cancer (AJCC) stages I–III unilateral primary invasive breast cancer who received some or all of their treatment at one of eight NCCN participating centers (City of Hope Comprehensive Cancer Center, Dana-Farber Cancer Institute, Fox Chase Cancer Center, H. Lee Moffitt Cancer Center, University of Texas M.D. Anderson Cancer Center, Ohio State University Comprehensive Cancer Center, Roswell Park Cancer Institute and University of Michigan Comprehensive Cancer Center) between July 1st 1997 to December 31st 2006 and who received their care at the participating institution for at least 365 days after their first

visit date. The institutional review boards at each center approved the protocol, data collection processes, data transmission methods, and data repository protocols. For centers requiring project-specific informed consent, only patients who provided informed consent were included in this analysis.

In order to identify a study cohort for whom adjuvant chemotherapy would constitute appropriate care, we classified all patients based on whether the relevant NCCN guideline: (1) recommended adjuvant chemotherapy ("chemotherapy as standard-of-care group"); (2) recommended consideration of adjuvant chemotherapy ("chemotherapy discretionary group"); or (3) recommended against adjuvant chemotherapy. The classification was performed using the guideline in effect at the time of each patient's diagnosis. Patients in the first two groups were eligible for this analysis (n=10,971). We excluded women who were older than 70 years (n=1,047) because NCCN guidelines note that there are insufficient data to define chemotherapy recommendations for this cohort of women. Patients with missing height and weight at diagnosis were also excluded (n=397). The final study population consisted of 9,527 breast cancer patients.

Data Elements

The NCCN Breast Cancer Outcomes Database contains detailed information on patient (race/ethnicity, age at diagnosis, co-morbidity score, income, treatment center), clinical (height and weight at diagnosis, chemotherapy and endocrine treatment, surgery type) and tumor (clinical and pathologic stage, estrogen receptor (ER) and progesterone receptor (PR) status, histology, nuclear/histologic grade, Her2/*neu* status) characteristics at diagnosis, abstracted from medical records by trained, dedicated abstractors. The data collection methods and the data quality assurance processes have previously been described [24]. In this database, comorbidity score at presentation to the NCCN center is assigned using either the Charlson index (determined by chart review) [25] or the modified version of this index developed by Katz et al (based on a patient survey)[26]. Self-designated race and ethnicity are recorded on patient surveys as non-Hispanic whites, non-Hispanic Black, Hispanic and other. For this analysis, the zip code of the patient's residence was linked to the 2000 Census data to estimate the median household income (U.S Census 2000, Summary File 3).

Statistical Methods

Pearson's χ^2 test and student's t test were used to test for distribution differences between patient and tumor characteristics for categorical and continuous variables, respectively. Body mass index was calculated as weight (kg)/(height (m^2)) and groups were separated into categories of underweight (BMI<18.5), normal (BMI ≥ 18.5 and <25), overweight (BMI ≥ 25 and <30), obese (BMI ≥ 30 and < 40) and extremely obesity (BMI ≥ 40) as described by the National Institutes of Health/National Heart, Lung and Blood Institute [27]. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression analysis in order to evaluate the association between BMI status at diagnosis and receipt of chemotherapy separately for the chemotherapy-standard of care and chemotherapy-discretionary groups.

Initially, univariable models were fit to evaluate the predictive main effect of each variable and a p-value threshold of ≤0.1 was used to select variables for inclusion in the multivariable models. A step-wise selection procedure was used to determine the most parsimonious multivariable model with a p-value ≤0.05 for the likelihood ratio test. Variables included in the evaluation of the association between BMI and receipt of chemotherapy included age at diagnosis (<50 years, 50–59 years, 60–70 years), race/ethnicity, income status, comorbidity score (0 versus ≥ 1), hormone receptor status (positive [estrogen receptor (ER) and/or progesterone receptor (PR-positive], negative [ER and PR-

negative]), *Her2neu* status (negative, positive, unknown), nuclear/histologic grade (low, intermediate and high grade tumors), histology and stage at diagnosis. In our analyses involving race/ethnicity, we used the non-Hispanic black group as the reference group (and not the larger non-Hispanic white group) in order to better demonstrate differences between non-Hispanic white and non-Hispanic black, as well as Hispanic and non-Hispanic black race/ethnicity groups. Interactions between the clinical covariates and BMI, age, ethnicity and comorbidity score were investigated in the regression models using the p-value of the Wald statistic for each interaction and any significant interactions were included in the final model. All reported p-values are two-sided, and p-values ≤0.05 were considered statistically significant. Model goodness-of-fit was assessed using the Hosmer-Lemeshow goodness-of-fit test and the assumption of fit was not violated for the final multivariable models and only those final variables (including interactions) that resulted in a good-fit model were retained. Analyses were performed using SAS for Windows (release 9.1; SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient, Clinical and Tumor Characteristics

Table 1 lists the overall patient and tumor characteristics of the patients included in the primary analysis. Ninety-two percent of patients in the study cohort were classified as “chemotherapy-standard-of-care”, and eight percent as “chemotherapy-discretionary”. In these groups, 14% and 49% of patients did not receive chemotherapy, respectively. Women younger than age 50 accounted for 49% of the study cohort in the chemotherapy-standard-of-care group and 38% in the chemotherapy-discretionary group. The majority of patients in the overall study cohort were non-Hispanic white (81%); non-Hispanic Black and Hispanic women accounted for 8% and 7% of the study cohort, respectively. The proportion of women who were overweight, obese or extremely obese was similar in the chemotherapy-standard-of-care and chemotherapy-discretionary groups (61% and 56%, respectively). As expected, there was a higher proportion of patients with stage I disease in the chemotherapy-discretionary group (82%) compared to the chemotherapy-standard-of-care group (25%).

Univariable Analyses of Receipt of Chemotherapy

In univariable analysis, BMI was significantly associated with receipt of chemotherapy among obese (OR 0.83, 95% CI 0.70–0.97) and extremely obese patients (OR 0.72; 95% CI 0.54–0.95) compared to normal weight patients in the chemotherapy-standard-of-care group. In the chemotherapy-discretionary group, overweight (HR 0.76, 95% CI 0.59–0.99) and obese patients (HR 0.73, 95% CI 0.55–0.98) were less likely to receive chemotherapy compared to normal weight patients, but there was no significant association for patients with extreme obesity (Table 2). Other patient-related factors associated with decreased receipt of chemotherapy in both the chemotherapy-standard-of-care and chemotherapy-discretionary groups included older age ($p<.001$) and the presence of comorbidity ($p<.001$). In the chemotherapy-standard-of-care group, Hispanic patients were statistically significantly more likely to receive chemotherapy compared to non-Hispanic Black patients (HR 1.50, 95% CI 1.05–2.14). Tumor characteristics including stage, hormone-receptor status, *Her2neu* status and nuclear grade were statistically significantly associated with receipt of chemotherapy (Table 2).

Multivariable Analysis of Patient-Related Factors and Receipt of Chemotherapy

In multivariable analysis, BMI was not associated with receipt of chemotherapy in either the chemotherapy-standard-of-care ($p=0.52$) (Table 3) or chemotherapy-discretionary group ($p=0.58$) (Table 4). Increasing age remained statistically significantly associated with receipt of chemotherapy for both groups, with women aged 60–70 being 90% less likely to receive

chemotherapy. In the chemotherapy-standard-of-care group, both non-Hispanic white and Hispanic patients were approximately 2-fold more likely to receive chemotherapy compared to non-Hispanic Black patients (OR 1.70, 95% CI 1.26–2.30 and OR 2.08, 95% CI 1.34–3.21, respectively) and the presence of comorbidity was statistically significantly associated with a 32% lower likelihood of receiving chemotherapy. There was no significant interaction between BMI and either comorbidity or race and receipt of chemotherapy.

Discussion

In a large, multi-institutional cohort of patients with operable breast cancer, we found that obesity had no effect on the receipt of adjuvant chemotherapy. Contrary to our expectations, this was true even among patients for whom the use of chemotherapy would be considered discretionary. There was also no evidence that obesity played a role in modifying the relationship between ethnicity or the presence of comorbidity and receipt of adjuvant chemotherapy.

To our knowledge, there has been one prior study investigating the relationship between BMI at breast cancer diagnosis and receipt of adjuvant systemic therapy [20]. Buist et al. evaluated a cohort of 897 women age ≥ 65 years diagnosed with early stage breast cancer within six health care organizations and found no association between BMI status and receipt of adjuvant systemic therapy. However, only 60% of women received any adjuvant systemic therapy and even fewer (18%) received chemotherapy. Our study confirms this observation in a much larger population, age ≤70, and limited to patients who met NCCN clinical guidelines for receipt of adjuvant chemotherapy. Furthermore, because of the very rich clinical data available in the NCCN database, we were able to distinguish between patients for whom the benefits of chemotherapy were more and less well-established. The fact that we found no effect of obesity on adjuvant therapy decisions in either group is reassuring as it suggests that patients who have the most to gain from adjuvant therapy are no less likely to receive as a result of their obesity. It also suggests that physicians are not influenced by patient weight even when treatment choice is based on clinical judgment.

We found that non-Hispanic Black patients were less likely to receive chemotherapy in the standard-of-care group compared to both non-Hispanic White and Hispanic patients, controlling for other patient and tumor characteristics. Our finding is consistent with population-based studies[3], [7], [11] and suggests that access to care does not fully account for racial disparities in treatment choice[28]. We did not find evidence for an interaction between obesity and the presence of co-morbidity that might partially explain the decreased receipt of chemotherapy among non-Hispanic black patients. Further investigation into the factors that affect the delivery of appropriate cancer care among non-Hispanic Black patients in academic centers is needed to improve the ethnic disparities that exist in breast cancer treatment and survival [29].

There are several limitations to our analyses. First, the study population was drawn from comprehensive cancer centers, and the results may not be generalizable to the general oncology community. Indeed, the prevalence of BMI ≥ 30kg/m2 in the study cohort (29%) was lower than the 35% rate of obesity in the United States[15], suggesting that the referral bias of the NCCN centers may have resulted in a healthier and possibly more compliant cohort of patients than the general population. It is possible that these centers have greater availability of supportive medical services for the management of co-existing co-morbidities and complications from treatment, better enabling them to safely provide chemotherapy to obese patients. We were also unable to evaluate whether receipt of chemotherapy among obese patients was accompanied by dose reductions or the early termination of treatment, since those data are not included in the NCCN database. Retrospective studies of

randomized trials have shown that dose-reducing chemotherapy results in decreased breast cancer failure-free survival[16], [17], [18], [19] and although early termination of chemotherapy is more common among Black compared to White women, an association with obesity has not been investigated [3].

Analysis of data from clinical trials has suggested that obese women with breast cancer are no more likely to suffer adverse events during standard dose adjuvant chemotherapy [19] and a recent review of the literature concluded that there is very little data to support the practice of deferring chemotherapy or limiting the dose of chemotherapy for patients with even extreme obesity [30]. Greenman et al. recommended that given the increase in prevalence of obesity and extreme obesity, guideline-development groups should provide information on standard of care practices for dosing obese breast cancer patients who are receiving adjuvant chemotherapy [31]. This study provides preliminary evidence that in a select clinical setting, physician recommendations regarding use of adjuvant chemotherapy for breast cancer are not influenced by patient weight. These study results also suggest that the demonstrated association between obesity and poorer breast cancer outcomes[32], [33] may not be related to obesity-related disparities in the decision to use adjuvant chemotherapy. The investigation of patient- related factors that contribute to disparities in receipt of adjuvant chemotherapy is necessary in order to translate clinical advances in the safety and effectiveness of adjuvant chemotherapy into the improved survival of patients with early stage breast cancer.

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Abbreviations

NCCN	National Comprehensive Cancer Network
BMI	body mass index
EBCTCG	The Early Breast Cancer Trialists's Collaborative Group
AJCC	American Joint Committee on Cancer
ER	estrogen receptor
PR	progesterone receptor
ORs	odds ratios
CIs	confidence intervals

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Table 1

Patient and Tumor Characteristics of Study Population (n=9,527)

Factors	Chemotherapy-standard-of-care N=8,219 %	Chemotherapy-discretionary N=1,308 %
Received Chemotherapy		
Yes	86	51
No	14	49
Age at Diagnosis		
<50	49	38
50–59	31	34
60–70	20	28
Race/Ethnicity		
White non Hispanic	80	85
Black non Hispanic	8	6
Hispanic	7	6
Other	5	3
Body mass index		
Underweight	1	2
Normal weight	38	42
Overweight	31	31
Obese	25	22
Extreme Obese	5	3
Co-morbidity score		
0	85	84
≥1	15	16
Census tract income level (median=$46,380)		
Above median	47	49
Below median	48	47
Missing	5	4
Stage at diagnosis		
I	25	82
II	62	18
III	13	-
Hormone receptor status		
ER+ or PR+	70	99
ER− and PR−	30	-
Missing	-	1
Her2neu status		
Positive	17	12
Negative	74	80

Factors	Chemotherapy-standard-of-care N=8,219 %	Chemotherapy-discretionary N=1,308 %
Unknown	9	8
Nuclear grade		
High or Intermediate	89	84
Low	7	11
Missing	4	5
Histology		
Invasive ductal/lobular	98	100
Tubular/papillary/medullary/colloid	2	-

Table 2

Univariate Models of Patient and Tumor Characteristics and Receipt of Chemotherapy

	Chemotherapy-standard-of-care		Chemotherapy-discretionary	
	Odds Ratio (95% CI)	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Factors			--	
Body mass index		0.02		0.12
Normal	Reference		Reference	
Underweight	1.54 (0.77–3.08)		0.64 (0.28–1.49)	
Overweight	0.88 (0.75–1.02)		0.76 (0.59–0.99)	
Obese	0.83 (0.70–0.97)		0.73 (0.55–0.98)	
Extreme obese	0.72 (0.54–0.95)		1.08 (0.59–1.99)	
Age at diagnosis		<.001		<.001
<50	Reference		Reference	
50–59	0.38 (0.32–0.45)		0.34 (0.26–0.45)	
60–70	0.13 (0.11–0.15)		0.08 (0.06–0.11)	
Ethnicity		0.005		0.77
Non-Hispanic Black	Reference		Reference	
Non-Hispanic White	0.91 (0.72–1.15)		1.29 (0.80–2.07)	
Hispanic	1.50 (1.05–2.14)		1.27 (0.68–2.39)	
Other	1.07 (0.73–1.58)		1.31 (0.60–2.89)	
Co-morbidity score		<.001		<.001
0	Reference		Reference	
≥1	0.50 (0.43–0.58)		0.60 (0.44–0.81)	
Census tract income level (median=$46,380)		0.07		0.66
Below median	Reference		Reference	
Above median	1.00 (0.89–1.14)		0.95 (0.76–1.18)	
Missing	1.51 (1.06–2.15)		1.23 (0.68–2.22)	
Stage at diagnosis		<.001		<.001
I	Reference		Reference	
II	7.15 (6.23–8.22)		10.55 (6.89–16.14)	
III	41.9 (24.54–71.55)		-	
Hormone receptor status		<.001		0.50
Negative	Reference			
Positive	0.22 (0.18–0.27)		Reference	
Unknown	0.13 (0.05–0.35)		0.65 (0.18–2.30)	
***Her2neu* status**		<.001		<.001
Negative	Reference		Reference	
Positive	4.78 (3.64–6.28)		3.39 (2.32–4.96)	
Unknown	1.92 (1.48–2.49)		1.06 (0.70–1.59)	
Missing				

	Chemotherapy-standard-of-care		Chemotherapy-discretionary	
	Odds Ratio (95% CI)	**P-value**	**Odds Ratio (95% CI)**	**P-value**
Nuclear/histologic grade		<.001		0.05
Low	Reference		Reference	
High or Intermediate	3.79 (3.14–4.57)		1.41 (0.99–2.01)	
Missing	3.08 (2.13–4.44)		1.95 (1.08–3.53)	
Histology		0.53		-
Invasive ductal/lobular	Reference		-	
Tubular/papillary/medullary/colloid	0.86 (0.54–1.38)			

Table 3

Multivariable Model of Patient Characteristics and Receipt of Chemotherapy for Chemotherapy-standard-of-care Group

	Odds Ratio* (95% CI)	P-value
Factors		
Body mass index		0.52
Normal	Reference	
Underweight	1.83 (0.80–4.16)	
Overweight	0.99 (0.82–1.20)	
Obese	1.08 (0.88–1.34)	
Extreme obese	0.92 (0.65–1.33)	
Age at diagnosis		<.001
<50	Reference	
50–59	0.38 (0.31–0.47)	
60–70	0.09 (0.08–0.12)	
Ethnicity		0.002
Non-Hispanic Black	Reference	
Non-Hispanic White	1.70 (1.26–2.30)	
Hispanic	2.08 (1.34–3.21)	
Other	1.52 (0.94–2.46)	
Co-morbidity score		<.001
0	Reference	
≥1	0.68 (0.56–0.83)	

*Controlling for nuclear/histologic grade, Her2neu status, interaction between stage and hormone-receptor status and National Comprehensive Cancer Network center.

Table 4

Multivariable Model of Patient Characteristics and Receipt of Chemotherapy for Chemotherapy-discretionary Group

	Odds Ratio* (95% CI)	**P-value**
Factors		
Body mass index		0.58
Normal	Reference	
Underweight	0.52 (0.19–1.44)	
Overweight	0.98 (0.71–1.36)	
Obese	1.15 (0.80–1.66)	
Extreme obese	1.27 (0.60–2.70)	
Age at diagnosis		<.001
<50	Reference	
50–59	0.31 (0.23–0.42)	
60–70	0.06 (0.04–0.09)	

*Controlling for Her2/neu status, stage and National Comprehensive Cancer Network center