

Obesity and Angiolymphatic Invasion in Primary Breast Cancer

Erin F. Gillespie¹, Melony E. Sorbero, PhD, MS, MPH², David A. Hanauer, MD, MS³, Michael S. Sabel, MD⁴, Emily J. Herrmann⁵, Laura J. Weiser⁵, Christina H. Jagielski, MPH⁶, and Jennifer J. Griggs, MD, MPH⁷

¹University of Michigan Medical School, Ann Arbor, MI; ²RAND Corporation, Pittsburgh, PA; ³Department of Pediatrics, Bioinformatics Core, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; ⁴Department of General Surgery, Division of Surgical Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; ⁵University of Michigan, Ann Arbor, MI; ⁶Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan Medical School, Ann Arbor, MI; ⁷Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI

ABSTRACT

Background. Obesity is associated with poorer breast cancer-specific survival. The purpose of this study was to investigate the relationships between obesity and the presence of angiolymphatic invasion as well as other features of invasive breast cancer, including stage at presentation, estrogen receptor (ER) status, triple-negative phenotype, and tumor grade.

Methods. Detailed clinical and pathologic data were abstracted from the medical records of all 1,312 patients with stage I–III primary breast cancer who had breast surgery at the University of Michigan Comprehensive Cancer Center between January 1, 2000 and December 31, 2006. Bivariate and multivariate analyses were conducted to investigate the relationships between body mass index and tumor biologic features, controlling for menopausal status, diabetes and hypertension, hormone replacement therapy before diagnosis, race, and ethnicity.

Results. In multivariate analyses, severe obesity was independently associated with the presence of angiolymphatic invasion [odds ratio (OR) 1.80, 95% confidence interval (CI) 1.08–2.99, joint test of significance, $P = 0.03$]. Severe obesity was associated with lower likelihood of triple-negative breast cancer (OR 0.39, 95% CI 0.16–0.96). Among premenopausal women with diabetes, ER-negative (OR

5.22, 95% CI 1.12–24.29) and triple-negative (OR 14.8, 95% CI 1.92–113.91) disease was significantly more common.

Discussion. In this large sample of invasive breast cancers, obesity was independently associated with the presence of angiolymphatic invasion. Higher rates of angiolymphatic invasion among obese women may account in part for poorer outcomes among obese women with breast cancer.

Obesity is associated with both higher rates of breast cancer and unfavorable breast cancer outcomes.^{1–9} Hazard ratios for long-term (10 years or more) breast cancer-specific mortality among obese women compared with healthy weight women range from 1.34 (95% CI 1.09–1.65) to 2.1 (95% CI 1.5–2.9).^{8,10}

Explanations for the poorer survival rates among obese women with breast cancer include more advanced disease at presentation (in part related to lower rates of screening mammography), systematic underdosing of adjuvant chemotherapy, and higher rates of diabetes and hypertension, each of which has been associated with unfavorable breast cancer outcomes.^{11–18}

Unfavorable tumor biology in obese women may also contribute to poorer outcomes. In a population-based study of 1,177 women, obese women under the age of 45 years were found to have higher histologic grade and a higher likelihood of estrogen receptor (ER)-negative tumors.¹⁰ Triple-negative breast cancers—negative for expression of ER, progesterone receptors (PR), and human epidermal growth factor-2 receptor (HER2)—are associated with a worse prognosis and have been shown in some.^{19–21} but not all²² studies to be more prevalent among obese women. Finally, diabetes has been associated with a higher likelihood of ER-negative breast cancer; the higher rate of diabetes among obese women may thus contribute to

differences in tumor biology among obese women compared with lean women.²³

Angiolymphatic invasion, defined as the presence of tumor cells in peritumoral lymphatics or blood vessels and associated with a higher risk of breast cancer recurrence, may also be more common in the breast cancers of obese women.^{24–27} The adipocytokines, cytokines produced by adipose tissue, may have proangiogenic effects, promoting vascular proliferation.²⁸ In one study of 393 patients, presence of angiolymphatic invasion was more often identified among women weighing over 80 kg. In logistic regression, angiolymphatic invasion was independently associated with nodal status, histologic grade, weight, and height.²⁹ Those investigators did not, however, control for other factors associated with tumor biology, such as estrogen receptor status or diabetes. Information on presence or absence of angiolymphatic invasion is largely missing from studies of breast cancer prognosis in obese women. In a recent study of 26 patients, body mass index was similarly associated with angiolymphatic invasion.³⁰

The purpose of this study was to investigate the relationship between obesity status, measured as body mass index (BMI), and tumor biologic features among women with breast cancer. We sought to characterize the independent association of obesity with the presence of angiolymphatic invasion, hormone receptor (ER and PR) status, HER2 status, stage, and tumor grade, after controlling for age, menopausal status, use of hormone replacement therapy (HRT), and diabetes and hypertension. We were particularly interested in the relationship between obesity and the prevalence of angiolymphatic invasion in primary breast cancers.

MATERIALS AND METHODS

Patient Selection

All adult female patients 21 years of age and older who had surgery for a primary stage I, II, or III breast cancer at the University of Michigan Comprehensive Cancer Center between January 1, 2000 and December 31, 2006 were eligible for inclusion. Pregnant women and women with occult breast primary tumor, metaplastic carcinoma or inflammatory breast cancer were excluded. After the sample was selected, we further excluded women who were on tamoxifen for breast cancer prevention at time of diagnosis ($n = 2$), patients who had had more than one primary within the breast ($n = 35$), patients treated on an institutional protocol of cryoablation ($n = 7$), and patients treated with primary endocrine therapy ($n = 5$).

Data Collection

Detailed medical record review was conducted to obtain information regarding age at diagnosis, race, ethnicity, menopausal status, use of systemic hormone replacement therapy in the year(s) before diagnosis of breast cancer, height and weight at the time of diagnosis, presence of diabetes or hypertension, and tumor pathologic characteristics (tumor size, lymph node status, histologic grade, ER status, PR status, HER2 status, and presence of angiolymphatic invasion). For patients in whom menopausal status was unknown, age over 50 years was used as a proxy for postmenopausal status. Height and weight, collected by a second abstractor who was blinded to tumor and clinical characteristics, was obtained from the electronic medical record. BMI was calculated using the Quetelet Index and categorized according to World Health Organization criteria as shown in Table 1.³¹ Continuous quality checks of the data were performed.

Analyses

Descriptive statistics were generated for each of the independent and dependent variables. Tumor size, and thus pathologic stage, was not determined for patients who received primary systemic chemotherapy therapy. Clinical and pathologic tumor features were compared between BMI categories using chi-squared tests. In patients who received primary systemic chemotherapy ($n = 199$), we report the tumor characteristics of the core biopsy specimen.

Separate multivariate logistic analyses were performed to identify predictors of ER-negative disease, triple-negative (ER-, PR-, and HER2-negative) phenotype, grade 3 histology, presence of angiolymphatic invasion, and stage III disease. The independent variables for each of these analyses were menopausal status, race, ethnicity, obesity status, diabetes, hypertension, and use of hormone replacement therapy. Age was collinear with menopausal status in preliminary analyses and was thus dropped in the multivariate analyses. Analyses were repeated according to menopausal status (pre/perimenopausal versus postmenopausal). For obesity, joint tests of significance were performed across categories. If the value of the dependent variable was unknown, those tumors were dropped from that analysis but retained for other analyses. Thus, the sample size for each multivariate analysis did not always sum to 1,312.

The Institutional Review Board at the University of Michigan approved all study procedures.

TABLE 1 Sample characteristics

	All		Healthy weight (BMI < 25 kg/m ²)		Overweight (BMI 25–29.9 kg/m ²)		Obese (BMI 30–34.9 kg/m ²)		Severely obese (BMI ≥ 35 kg/m ²)		P-Value
	N = 1,312		N = 502		N = 404		N = 232		N = 174 (13.3%)		
Mean age, years (SD)	55.3	(12.5)	52.8	(12.9)	55.9	(12.7)	58.5	(11.5)	56.4	(10.8)	<0.001
	N	%	N	%	N	%	N	%	N	%	
Race											<0.001
White	1,158	88.3	443	88.3	365	90.4	210	90.5	140	80.5	
Black	77	5.9	14	2.8	21	5.2	18	7.8	24	13.8	
Asian/Pacific Islander	45	3.4	34	6.8	8	2.0	1	0.4	2.0	1.2	
Multiracial	3	0.2	1	0.2	1	0.3	0	0	1	0.6	
Unknown	29	2.2	10	2.0	9	2.2	3	1.3	7	4.0	
Ethnicity											0.22
Hispanic	25	1.9	7	1.4	11	2.7	6	2.6	1	0.6	
Non-Hispanic	1,287	98.1	495	98.6	393	97.3	226	97.4	173	99.4	
Menopausal status ^a											<0.001
Pre/perimenopausal	533	40.6	257	51.2	161	39.9	64	27.6	51	29.3	
Postmenopausal	779	59.4	245	48.8	243	60.2	168	72.4	123	70.7	
Comorbidity											
Hypertension	425	32.4	87	17.3	121	30.0	108	46.6	109	62.6	<0.001
Diabetes mellitus	101	7.7	11	2.2	21	5.2	29	12.5	40	23.0	<0.001
Type 1	9	8.9	2	18.2	1	4.8	2	6.9	4	10.0	0.61
Type 2	92	91.1	9	81.8	20	95.2	27	93.1	36	90.0	
Insulin	20	21.7	1	11.1	2	10.0	5	18.5	12	33.3	0.16
HRT	457	34.8	162	32.3	141	34.9	88	37.9	66	37.9	0.37
Primary systemic therapy											
Chemotherapy	199	15.2	70	13.9	73	18.1	35	15.1	21	12.1	0.15

HRT hormone replacement therapy

P values are chi-square tests except for weight, which is an F-test from analysis of variance (ANOVA)

^a In forty-four patients menopausal status unknown; age was used for assignment of menopausal status (see text)

RESULTS

Sample Characteristics

Our sample included 1,312 patients. Table 1 shows the sample characteristics for the entire sample and by obesity status. Most (88.3%) of the patients were non-Hispanic Whites. Mean age was 55.3 years [standard deviation (SD) 12.5 years]. Diabetes was present in 7.7% of the sample, and 32.4% of the tumors developed in patients who carried a diagnosis of hypertension. Hypertension ($P < 0.001$) and diabetes ($P < 0.001$) were significantly associated with increasing BMI. Insulin use did not differ according to BMI category. For 44 tumors, patient menopausal status was unknown, and in those patients we used age over 50 years as a proxy for menopausal status as described above. Hormone replacement therapy (HRT) at time of the diagnosis was documented in 34.8%, with no difference in rates of HRT use according to BMI category.

Obesity and Stage of Disease

The majority (79.0%) of cancers were pathologic stage I or II. As described above, patients who received primary systemic chemotherapy ($n = 199$) were excluded from this portion of the analysis because pathologic tumor measurement before resection could not be determined. There was no association between stage and obesity status.

Obesity and Tumor Biology

In bivariate analyses (Table 2), obesity was not associated with hormone receptor status, HER2 status, triple-negative phenotype, or histologic grade. There was a significant association between obesity category and presence of angiolymphatic invasion ($P = 0.03$), severely obese women being the most likely to have angiolymphatic invasion. When the analysis was repeated by menopausal status, the likelihood of angiolymphatic invasion in the

TABLE 2 Stage and tumor biologic characteristics ($N = 1,398$)

	Normal weight		Overweight		Obese		Severely obese		P-Value
	$N = 523$		$N = 430$		$N = 255$		$N = 190$		
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%	
AJCC 2003 stage									0.58
I	268	53.4	206	51.0	128	55.2	90	51.7	
II	138	27.5	104	25.7	56	24.1	47	27.0	
III	21	4.2	16	4.0	12	5.2	13	7.5	
Unknown	10	2.0	10	2.5	3	1.3	5	2.9	
Clinical stage II–III ^a	65	13.0	68	16.8	33	14.2	19	10.9	
Tumor size (cm), mean (SD) ^b	1.5	(1.1)	1.6	(1.1)	1.5	(1.3)	1.7	(1.5)	0.35
ER status									0.70
Positive	351	69.9	291	72.0	165	71.1	132	75.9	
Negative	132	26.3	102	25.3	62	26.7	37	21.3	
Unknown	19	3.8	11	2.7	5	2.2	5	2.9	
PR status									0.24
Positive	263	52.4	236	58.4	129	55.6	110	63.2	
Negative	219	43.6	157	38.9	96	41.4	60	34.5	
Unknown	20	4.0	11	2.7	7	3.0	4	2.3	
HER2 status									0.48
Positive	87	17.3	76	18.8	36	15.5	21	12.1	
Negative	392	78.1	312	77.2	189	81.5	145	83.3	
Unknown	23	4.6	16	4.0	7	3.0	8	4.6	
Triple negative									0.20
Yes	42	8.4	24	5.9	12	5.2	7	4.0	
Unknown	28	5.6	18	4.5	7	3.0	10	5.8	
Angiolymphatic invasion									0.03
Yes	69	13.8	71	17.6	26	11.2	36	20.7	
No	433	86.3	333	82.4	206	88.8	138	79.3	
Grade									0.75
1	110	21.9	66	16.3	43	18.5	37	21.3	
2	215	42.8	194	48	101	43.5	76	43.7	
3	130	25.9	106	26.2	65	28	46	26.4	
Unknown	47	9.4	38	9.4	23	9.9	15	8.6	

AJCC American Joint Committee on Cancer

^a Treated with primary systemic chemotherapy, $n = 199$

^b Excludes patients treated with primary systemic chemotherapy

tumors varied by obesity category ($P = 0.05$), with angiolymphatic invasion more likely in severely obese (21.6%) compared with the tumors of healthy weight (14.8%) women (data not shown) among the pre- and perimenopausal women.

In multivariate analyses (Table 3), obesity status was independently associated with presence of angiolymphatic invasion (joint test of significance, $P = 0.03$) after controlling for menopausal status, use of hormone replacement therapy at the time of diagnosis, diabetes and hypertension, and tumor features, including grade, stage, estrogen receptor status, and HER2 status. Grade was also associated with

angiolymphatic invasion (OR, for grade 2 was 5.12, 95% CI 2.61–10.04; OR for grade 3 8.98, 95% CI 4.38–18.43). Obesity was associated with lower odds of triple-negative disease (OR among severely obese women 0.39, 95% CI 0.16–0.96). Obesity was not associated with other tumor features, including HER2 status (not shown in table).

There were significant associations between diabetes and tumor biology in multivariate analyses restricted to tumors in pre- and perimenopausal women (Table 4). Diabetes was associated with ER-negative tumor status (OR 5.22, 95% CI 1.12–24.29) and with triple-negative phenotype (OR 14.80, 95% CI 1.92–113.91).

TABLE 3 Multivariate analyses

	Stage III N = 1,247 OR (95% CI)	Grade III N = 1,189 OR (95% CI)	ER-negative N = 1,272 OR (95% CI)	Triple-negative N = 979 OR (95% CI)	Angiolymphatic invasion N = 1,312 OR (95% CI)
Menopausal status					
Pre/ peri	Referent	Referent	Referent	Referent	Referent
Post	0.84 (0.44–1.60)	0.80 (0.55–1.17)	0.97 (0.67–1.41)	1.24 (0.70–2.22)	0.80 (0.54–1.18)
Race					
White	Referent	Referent	Referent	Referent	Referent
Black	0.91 (0.31–2.69)	2.55 (1.40–4.66)^b	0.90 (0.49–1.65)	0.46 (0.14–1.57)	1.20 (0.64–2.25)
Asian/Pacific Islander	1.43 (0.42–4.93)	0.94 (0.40–2.19)	0.62 (0.25–1.52)	0.82 (0.23–2.86)	1.23 (0.54–2.78)
Unknown	2.62 (0.86–7.94)	1.14 (0.46–2.82)	1.31 (0.54–3.22)	2.22 (0.76–6.46)	2.18 (0.97–4.88)
Ethnicity					
Hispanic	(Dropped)	0.96 (0.31–2.94)	1.24 (0.44–3.52)	(Dropped)	0.52 (0.12–2.31)
Non-Hispanic	Referent	Referent	Referent	Referent	Referent
Obesity status					
Normal weight	Referent	Referent	Referent	Referent	Referent
Overweight	0.99 (0.50–1.95)	1.12 (.77–1.61)	0.89 (0.62–1.27)	0.62 (0.36–1.08)	1.36 (0.93–1.99)
Obese	1.36 (0.63–2.93)	1.28 (0.82–1.99)	0.97 (0.63–1.50)	0.51 (0.25–1.03)	0.84 (0.51–1.40)
Severely obese	1.85 (0.83–4.11)	1.26 (0.76–2.09)	0.75 (0.44–1.26)	0.39 (0.16–0.96)^a	1.80 (1.08–2.99)^a
Joint test for significance for obesity category					
	P = 0.40	P = 0.69	P = 0.70	P = 0.08	P = 0.03
Test for trend					
	P = 0.12	P = 0.25	P = 0.39	P = 0.02	P = 0.14
Diabetes	1.46 (0.59–3.61)	0.67 (0.36–1.23)	1.16 (0.63–2.12)	2.03 (0.85–4.86)	1.27 (0.69–2.32)
Hypertension	0.85 (0.44–1.65)	1.01 (0.70–1.46)	0.68 (0.47–0.98)^a	0.82 (0.45–1.50)	0.75 (0.50–1.12)
HRT	0.73 (0.37–1.43)	0.82 (0.56–1.18)	1.12 (0.78–1.62)	0.96 (0.54–1.69)	0.98 (0.66–1.45)
ER status					
Positive	Referent	Referent	Referent	Referent	Referent
Negative	0.66 (0.33–1.31)	13.15 (9.63–17.96)^c		0.80 (0.54–1.29)	
Unknown	(Dropped)	2.09 (0.54–8.13)		0.26 (0.03–2.06)	
Grade					
1	Referent	Referent	Referent	(Dropped)	Referent
2	1.37 (0.63–2.97)		4.89 (2.41–9.92)^c	Referent	5.12 (2.61–10.04)^c
3	2.39 (1.00–5.68)^a		47.15 (23.28–95.50)^c	3.64 (2.25–5.88)^c	8.98 (4.38–18.43)^c
Unknown	0.32 (0.04–2.59)		8.88 (3.91–20.13)^c	0.22 (0.03–1.61)	1.02 (0.31–3.37)
HRT hormone replacement therapy					

^a P < 0.05

^b P ≤ 0.01

^c P ≤ 0.001

TABLE 4 Multivariate analyses, premenopausal only

	Stage III N = 463 OR (95% CI)	Grade III N = 478 OR (95% CI)	ER-negative N = 515 OR (95% CI)	Triple-negative N = 418 OR (95% CI)	Angiolympathic invasion N = 521 OR (95% CI)
Race					
White	Referent	Referent	Referent	Referent	Referent
Black	0.52 (0.06–4.45)	2.17 (0.76–6.25)	1.44 (0.49–4.24)	0.33 (0.03–3.49)	2.33 (0.89–6.13)
Asian/Pacific Islander	0.70 (0.09–5.60)	0.22 (0.06–0.86)^a	1.49 (0.49–4.52)	1.11 (0.21–5.87)	0.96 (0.31–3.03)
Unknown	2.28 (0.42–12.52)	1.20 (0.27–5.30)	2.58 (0.57–11.64)	5.29 (0.82–33.94)	3.11 (0.83–11.59)
Ethnicity					
Hispanic	Dropped	0.80 (0.14–4.39)	2.80 (0.67–11.61)	Dropped	Dropped
Non-Hispanic		Referent	Referent		
Obesity status					
Normal weight	Referent	Referent	Referent	Referent	Referent
Overweight	0.80 (0.30–2.09)	0.88 (0.52–1.51)	1.16 (0.69–1.95)	0.63 (0.27–1.43)	1.76 (1.04–2.99)^a
Obese	0.56 (0.12–2.63)	1.27 (0.61–2.62)	0.94 (0.45–1.98)	0.38 (0.10–1.50)	0.73 (0.31–1.75)
Severely obese	2.68 (0.88–8.12)	0.99 (0.41–2.38)	0.53 (0.20–1.37)	0.09 (0.01–0.97)^a	1.61 (0.69–3.76)
Joint test for significance for obesity category	P = 0.15	P = 0.84	P = 0.46	P = 0.15	P = 0.08
Test for trend	P = 0.27	P = 0.82	P = 0.36	P = 0.02	P = 0.45
Diabetes	1.29 (0.12–13.65)	0.08 (0.01–0.95)^a	5.22 (1.12–24.29)^a	14.80 (1.92–113.91)	0.54 (0.06–5.14)
Hypertension	1.29 (0.40–4.16)	1.00 (0.47–2.14)	0.46 (0.20–1.05)	1.44 (0.42–4.97)	0.70 (0.31–1.57)
HRT	1.42 (0.30–6.67)	2.40 (0.87–6.64)	0.83 (0.31–2.21)	0.45 (0.06–3.58)	0.54 (0.15–1.90)
ER status					
Positive	Referent	Referent	Referent		Referent
Negative	1.23 (0.47–3.23)	13.65 (8.32–22.39)^c			1.18 (0.66–2.10)
Unknown	Dropped	2.53 (0.45–14.30)			0.65 (0.07–5.75)
Grade					
1	Referent		Referent	Dropped	Referent
2	1.09 (0.33–3.55)		5.06 (1.48–17.31)^c	Referent	6.43 (1.93–21.49)^b
3	1.50 (0.41–5.59)		51.71 (15.19–176.02)^c	3.64 (1.67–7.95)^c	8.43 (2.38–29.84)^c
Unknown	Dropped		13.66 (3.56–52.41)^c	0.45 (0.05–3.84)	0.53 (0.05–5.45)

HRT hormone replacement therapy

^a P < 0.05

^b P ≤ 0.01

^c P ≤ 0.001

DISCUSSION

In summary, in this sample of 1,312 patients, severe obesity was associated with higher likelihood of angiolymphatic invasion after controlling for stage, grade, menopausal status, diabetes and hypertension, and use of HRT at the time of diagnosis. In pre- and perimenopausal women, diabetes was also independently associated with ER-negative status.²³ Triple-negative tumors were less common among the severely obese women in our sample.

Our results are consistent with those of other investigators demonstrating higher rates of angiolymphatic invasion in the tumors of heavy women.^{29,30} In contrast to other studies demonstrating higher rates of triple-negative breast cancer, the heavy patients in our sample were less likely to have triple-negative tumors.^{19–21} Obese women in our sample, as in others, are more likely to have diabetes.³² The association we identified between diabetes and triple-negative breast cancer raises the possibility that it is not obesity but rather diabetes that contributes to higher rates of triple-negative breast cancer in obese women.

Our sample is limited by low numbers of minority women and the lack of data on socioeconomic status (SES). Black race and lower SES have both been associated with ER-negative disease.^{33,34} Furthermore, Black race and Hispanic ethnicity have been associated with a higher likelihood of triple-negative breast cancer regardless of obesity status.^{22,35,36} It remains unknown whether there is a relationship between race, ethnicity, and SES and angiolymphatic invasion. Investigations of these relationships should include consideration of comorbid diabetes. In addition, our study is limited by the absence of information on exercise and dietary patterns and by the absence of information on duration of obesity and history of obesity among the non-obese.

Both estrogen-dependent and estrogen-independent mechanisms have been proposed as mechanisms for the association between obesity and poorer outcome.³⁷ Higher body mass index is associated with higher levels of bioavailable estradiol, which in turn facilitates tumor growth.^{38,39} Although not a finding in our study, obesity has been associated with higher likelihood of ER-negative disease by some authors.¹⁰ In addition, higher fasting insulin levels among obese people may lead to higher proliferative rates due to the mitogenic effects of insulin.⁴⁰ Finally, adipocytokines (also referred to as adipokines), such as leptin, tumor necrosis factor-alpha, and interleukin-6, are increased in obesity and are associated with increased cell proliferation and angiogenesis in animal models and in cell lines.^{28,41–43} The independent association of severe obesity with presence of angiolymphatic invasion in our sample supports the relationship between adipocytokines and angiolymphatic invasion in primary breast cancer.

Reductions in adiposity, whether achieved through diet, exercise or gastric reduction surgery, have been shown to reduce leptin and other adipocytokines.^{44–47} Such interventions may reduce the risk of breast cancer overall and, specifically, breast cancer exhibiting angiolymphatic invasion. Although a direct relationship between these interventions and rates of angiolymphatic invasion has not been identified, it is possible that the reduction in cancer mortality among obese patients having bariatric surgery can be attributed in part to reductions in adipocytokines.^{48,49}

In conclusion, this study has identified the independent association between severe obesity and presence of angiolymphatic invasion. These findings may help explain poorer outcomes among obese women with breast cancer. Furthermore, diabetes was identified as being independently associated with triple-negative breast cancer. Further study of the relationships between tumor biology, obesity, diabetes, race, ethnicity, and SES are warranted.

ACKNOWLEDGMENT Supported in part by the University of Michigan Medical School 2008 Student Biomedical Research Program (E.F.G.) and by NIH/NCI R01 CA922444-01 (J.J.G.).

REFERENCES

1. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: Cohort study. *BMJ*. 2007;335(7630): 1134.
2. Okasha M, McCarron P, McEwen J, Smith GD. Body mass index in young adulthood and cancer mortality: a retrospective cohort study. *J Epidemiol Community Health*. 2002;56(10):780–4.
3. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *NEJM*. 2003;348(17):1625–38.
4. Modugno F, Kip KE, Cochrane B, et al. Obesity, hormone therapy, estrogen metabolism and risk of postmenopausal breast cancer. *Int J Cancer*. 2006;118(5):1292–301.
5. Majed B, Moreau T, Senouci K, Salmon RJ, Fourquet A, Asselain B. Is obesity an independent prognosis factor in woman breast cancer? *Breast Cancer Res Treat*. 2008;111(2):329–42.
6. Majed B, Moreau T, Asselain B. Overweight, obesity and breast cancer prognosis: Optimal body size indicator cut-points. *Breast Cancer Res Treat*. 2009;115(1):193–203.
7. Dal Maso L, Zucchetto A, Talamini R, et al. Effect of obesity and other lifestyle factors on mortality in women with breast cancer. *Int J Cancer*. 2008;123(9):2188–94.
8. Whitman MK, Hillis SD, Curtis KM, McDonald JA, Wingo PA, Marchbanks PA. Body mass and mortality after breast cancer diagnosis. *Cancer Epidemiol Biomarkers Prev*. 2005;14(8):2009–14.
9. Abrahamson PE, Gammon MD, Lund MJ, et al. General and abdominal obesity and survival among young women with breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2006;15(10):1871–7.
10. Daling JR, Malone KE, Doody DR, Johnson LG, Gralow JR, Porter PL. Relation of body mass index to tumor markers and survival among young women with invasive ductal breast carcinoma. *Cancer*. 2001;92(4):720–9.
11. Maehle BO, Tretli S, Skjaerven R, Thorsen T. Premorbid body weight and its relations to primary tumour diameter in breast cancer patients; its dependence on estrogen and progesterone receptor status. *Breast Cancer Res Treat*. 2001;68(2):159–69.

12. Cui Y, Whiteman MK, Flaws JA, Langenberg P, Tkaczuk KH, Bush TL. Body mass and stage of breast cancer at diagnosis. *Int J Cancer*. 2002;98(2):279–83.
13. Loi S, Milne RL, Friedlander ML, et al. Obesity and outcomes in premenopausal and postmenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2005;14(7):1686–91.
14. Wee CC, McCarthy EP, Davis RB, Phillips RS. Obesity and breast cancer screening. *J Gen Intern Med*. 2004;19(4):324–31.
15. Griggs JJ, Sorbero ME, Lyman GH. Undertreatment of obese women receiving breast cancer chemotherapy. *Arch Intern Med*. 2005;165(11):1267–73.
16. Griggs JJ, Culakova E, Sorbero ME, et al. Effect of patient socioeconomic status and body mass index on the quality of breast cancer adjuvant chemotherapy. *J Clin Oncol*. 2007;25(3):277–84.
17. Lipscombe LL, Goodwin PJ, Zinman B, McLaughlin JR, Hux JE. The impact of diabetes on survival following breast cancer. *Breast Cancer Res Treat*. 2008;109(2):389–95.
18. Braithwaite D, Tammemagi CM, Moore DH, et al. Hypertension is an independent predictor of survival disparity between African-American and white breast cancer patients. *Int J Cancer*. 2009;124(5):1213–9.
19. Millikan RC, Newman B, Tse CK, et al. Epidemiology of basal-like breast cancer. *Breast Cancer Res Treat*. 2008;109(1):123–39.
20. Phipps AI, Malone KE, Porter PL, Daling JR, Li CI. Body size and risk of luminal, HER2-overexpressing, and triple-negative breast cancer in postmenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2008;17(8):2078–86.
21. Vona-Davis L, Rose DP, Hazard H, et al. Triple-negative breast cancer and obesity in a rural Appalachian population. *Cancer Epidemiol Biomarkers Prev*. 2008;17(12):3319–24.
22. Stead LA, Lash TL, Sobieraj JE, et al. Triple-negative breast cancers are increased in black women regardless of age or body mass index. *Breast Cancer Res*. 2009;11(2):R18.
23. Wolf I, Sadetzki S, Gluck I, et al. Association between diabetes mellitus and adverse characteristics of breast cancer at presentation. *Eur J Cancer*. 2006;42(8):1077–82.
24. Ejlertsen B, Jensen MB, Rank F, et al. Population-based study of peritumoral lymphovascular invasion and outcome among patients with operable breast cancer. *J Natl Cancer Inst*. 2009;101(10):729–35.
25. Schmidt M, Victor A, Bratzel D, et al. Long-term outcome prediction by clinicopathological risk classification algorithms in node-negative breast cancer—Comparison between Adjuvant!, St Gallen, and a novel risk algorithm used in the prospective randomized Node-Negative-Breast Cancer-3 (NNBC-3) trial. *Ann Oncol*. 2009;20(2):258–64.
26. Dhakal HP, Naume B, Synnestevedt M, et al. Vascularization in primary breast carcinomas: Its prognostic significance and relationship with tumor cell dissemination. *Clin Cancer Res*. 2008;14(8):2341–50.
27. Montagna E, Bagnardi V, Rotmensz N, et al. Factors that predict early treatment failure for patients with locally advanced (T4) breast cancer. *Br J Cancer*. 2008;98(11):1745–52.
28. Rose DP, Komninou D, Stephenson GD. Obesity, adipocytokines, and insulin resistance in breast cancer. *Obes Res*. 2004;5(3):153–65.
29. Badwe RA, Fentiman IS, Millis RR, Gregory WM. Body weight and vascular invasion in post-menopausal women with breast cancer. *Br J Cancer*. 1997;75(6):910–3.
30. Pfeiler G, Trecek O, Wenzel G, et al. Correlation of body mass index and menopausal status with the intra-tumoral estrogen system in invasive breast cancer. *Gynecol Endocrinol*. 2009;25(3):183–7.
31. National Heart Lung and Blood Institute. <http://www.nhlbi.support.com/bmi/>. Accessed June 1, 2008.
32. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. *BMC Public Health*. 2009;9:88.
33. Gapstur SM, Dupuis J, Gann P, Collila S, Winchester DP. (1996) Hormone receptor status of breast tumors in black, Hispanic, and non-Hispanic white women. An analysis of 13,239 cases. *Cancer* 77(8):1465–71.
34. Gordon NH. Association of education and income with estrogen receptor status in primary breast cancer. *Am J Epidemiol*. 1995;142(8):796–803.
35. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: A population-based study from the California cancer Registry. *Cancer*. 2007;109(9):1721–8.
36. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA*. 2006;295(21):2492–502.
37. Lorincz AM, Sukumar S. Molecular links between obesity and breast cancer. *Endocr Relat Cancer*. 2006;13(2):279–92.
38. Key TJ, Appleby PN, Reeves GK, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst*. 2003;95(16):1218–26.
39. McTiernan A, Rajan KB, Tworoger SS, et al. Adiposity and sex hormones in postmenopausal breast cancer survivors. *J Clin Oncol*. 2003;21(10):1961–6.
40. Goodwin PJ, Ennis M, Pritchard KI, et al. Fasting insulin and outcome in early-stage breast cancer: Results of a prospective cohort study. *J Clin Oncol*. 2002;20(1):42–51.
41. Garofalo C, Koda M, Cascio S, et al. Increased expression of leptin and the leptin receptor as a marker of breast cancer progression: possible role of obesity-related stimuli. *Clin Cancer Res*. 2006;12(5):1447–53.
42. Gonzalez RR, Cherfils S, Escobar M, et al. Leptin signaling promotes the growth of mammary tumors and increases the expression of vascular endothelial growth factor (VEGF) and its receptor type two (VEGF-R2). *J Biol Chem*. 2006;281(36):26320–8.
43. Cirillo D, Rachiglio AM, la Montagna R, Giordano A, Normanno N. Leptin signaling in breast cancer: An overview. *J Cell Biochem*. 2008;105(4):956–64.
44. Kotidis EV, Koliakos GG, Baltzopoulos VG, Ioannidis KN, Yovos JG, Papavramidis ST. Serum ghrelin, leptin and adiponectin levels before and after weight loss: comparison of three methods of treatment—a prospective study. *Obes Surg*. 2006;16(11):1425–32.
45. Irwin ML, McTiernan A, Bernstein L, et al. Relationship of obesity and physical activity with C-peptide, leptin, and insulin-like growth factors in breast cancer survivors. *Cancer Epidemiol Biomarkers Prev*. 2005;14(12):2881–8.
46. Trakhtenbroit MA, Leichman JG, Algham MF, et al. Body weight, insulin resistance, and serum adipokine levels 2 years after 2 types of bariatric surgery. *Am J Med*. 2009;122(5):435–42.
47. Garcia de la Torre N, Rubio MA, Bordiu E, et al. Effects of weight loss after bariatric surgery for morbid obesity on vascular endothelial growth factor-A, adipocytokines, and insulin. *J Clin Endocrinol Metab*. 2008;93(11):4276–81.
48. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med*. 2007;357(8):753–61.
49. Sjostrom L, Narbro K, Sjostrom CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med*. 2007;357(8):741–52.