

Body Weight Correlates With Mortality in Early-Stage Breast Cancer

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Hypothesis: Body weight correlates with risk of breast cancer death.

Design: A retrospective cohort study using patient medical records, electronic cancer registry data, and archived tissue specimens.

Setting: A 395-bed, comprehensive community hospital.

Patients: One thousand three hundred seventy-six women, aged 24 to 81 years, who were diagnosed with breast cancer between January 1, 1988, and December 31, 1995, and for whom complete medical records and adequate tissue specimens existed.

Main Outcome Measures: Body weight at the time of diagnosis and patient status (ie, alive and free of breast cancer, living with breast cancer, dead of breast cancer, or dead of other cause) at the time of longest follow-up. Additional data collected, including age at diagnosis, menopausal status, tumor size, tumor grade, lymph node status, stage at diagnosis, race, estrogen-receptor (ER) status, and treatment information, were used to create multivariate Cox proportional hazards models to estimate hazard rate (HR) ratios and 95% confidence intervals (CIs) for breast cancer death. We collected ER status from the patients' medical records, when available, and supplemented the information by using immunohistochemi-

cal techniques to determine ER status from archived paraffin-embedded tumor blocks.

Results: Patients were followed up for a median of 6.8 years after diagnosis. Two hundred forty-six patients died from breast cancer. Among patients with early-stage disease (I and IIA), we observed a dose-response relationship of increasing weight with increasing likelihood of dying of breast cancer. Compared with women in the lowest category of weight (<133 lb [60 kg] at diagnosis), women in the highest category (≥ 175 lb [79 kg]) experienced a 2.5-fold increased risk of dying from breast cancer (HR ratio, 2.54 [95% CI, 1.08-6.00]; trend $P = .02$). Women with ER-negative cancer experienced an approximately 2-fold higher risk of dying from breast cancer compared with women with ER-positive cancer, regardless of stage at diagnosis. Women in the upper 50th percentile of weight with early-stage disease and with ER-negative tumors had a nearly 5-fold increased risk of dying (HR ratio, 4.99 [95% CI, 2.17-11.48]; P for interaction = .10) compared with women in the lower 50th percentile of weight and ER-positive tumors. The results were similar for body mass index, a measure of obesity in which weight is adjusted for height.

Conclusion: Body weight at diagnosis and ER status are important predictors of breast cancer death in early-stage disease.

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NUMEROUS STUDIES HAVE examined the incidence of and, more recently, survival from breast cancer in relation to body size. Mounting epidemiological evidence suggests that postmenopausal breast cancer risk is higher among women with larger body size, as measured by body weight or body mass index (BMI), a measure of obesity in which weight is adjusted for height.¹ In contrast, for women who have not yet experienced menopause, breast cancer risk appears to be weakly inversely associated with body size, with the heaviest women

experiencing the lowest breast cancer risk compared with the thinnest women.¹ A growing body of evidence suggests that higher body weight at breast cancer diagnosis is associated with poorer breast cancer outcomes.²

To better understand the role of body weight on breast cancer outcome, we examined the association of body weight and breast cancer death in relation to other known breast cancer prognostic factors in a retrospective cohort study of patients with breast cancer from a large health maintenance organization in southern California.

METHODS

Eligible participants included all female health plan members who were diagnosed for the first time with histologically confirmed invasive breast cancer from January 1, 1988, through December 31, 1995, at the Kaiser Permanente San Diego Medical Center in California and who completed their first course of treatment within the health plan. We identified patients from the cancer registry database, and we confirmed patient eligibility with medical record review.

The main sources of data for this study were the cancer registry database, the patients' medical records, and mortality databases. We extracted from the cancer registry database patient information including age and race/ethnicity; tumor information including Surveillance, Epidemiology, and End Results and TNM stage at diagnosis, grade at diagnosis, lymph node status, tumor size, estrogen-receptor (ER) status, and histologic features; treatment information including type of surgery and use of chemotherapy, hormone therapy, or radiation therapy; and follow-up information including vital status at last follow-up.

We abstracted from the patients' medical records information on the patients' height, weight, family history, smoking status, parity, and menopausal status at diagnosis. We calculated BMI as the weight in kilograms divided by the height in meters squared. We confirmed some tumor information in the medical records including ER status and laterality. We obtained detailed information about the patients' surgical therapy, chemotherapy, hormone therapy, and radiation therapy, including reason for treatment, start and end dates, and dosages, when relevant. We abstracted detailed follow-up information, including recurrences (local and/or distant), sites of metastases, and occurrence of new primary tumors, vital status, and cause of death, if deceased. We reviewed the patients' medical records for information about significant comorbid conditions present at the time of the patient's diagnosis.

To identify deaths within the cohort and causes of death, we conducted a probabilistic linkage of the cohort with mortality data from the California State Death Certificate Master File, with information about deaths in the state of California through 2000. All matches were confirmed by manually reviewing the patient information from the mortality file with the patients' demographic information in the health plan files.

We obtained ER information from cancer registry files and from the patients' medical records. In addition, we collected archival paraffin-embedded tumor tissue and conducted immunohistochemical assays to confirm ER status and to provide ER information for patients with ER status missing in the medical record or cancer registry database.

Hazard rate (HR) ratios and 95% confidence intervals (CIs) were calculated to compare the likelihood of breast cancer death among patients in 1 category of exposure with a reference category. Multivariate models included factors known to be associated with breast cancer survival including age, grade, stage, tumor size, lymph node status, and ER status. Statistical analyses were performed by 1 of us (S.M.E.). Each of the authors reviewed the data and attests to its accuracy and completeness.

The study has been reviewed and approved by the Kaiser Permanente Medical Care Program, San Diego, Calif, institutional review board and by the institutional review board of the University of Southern California, Los Angeles, and was conducted according to the policies of the institutional review board.

RESULTS

We identified 1555 patients eligible for inclusion in the study based on cancer registry records. We completed medical record abstractions for 1465 patients (94.2%) of

Table 1. Characteristics of the Population*

	No. (%) of Patients
Age at diagnosis, y	
<50	454 (31.0)
≥50	1011 (69.0)
Histologic type	
Infiltrating ductal carcinoma	1099 (75.0)
Infiltrating lobular carcinoma	105 (7.2)
Other	261 (17.8)
Lymph node status	
Negative	903 (61.6)
Positive	556 (38.0)
Unknown	6 (0.4)
TNM stage at diagnosis	
I	737 (50.3)
II	4 (0.3)
IIA	379 (25.9)
IIB	196 (13.4)
IIIA	34 (2.3)
IIIB	47 (3.2)
IV	68 (4.6)
Tumor size, cm	
<2.0	970 (66.2)
≥2.0	434 (29.6)

*n = 1465.

the 1555 eligible patients. Of the 90 patients for whom medical record abstraction was not completed, 24 were missing vital status or cause of death and 66 had medical records that could not be located. One thousand three hundred seventy-six patients (88.5% of those eligible) also had complete ER information based on cancer registry files, medical records, or laboratory assays.

Almost one third of the patients (454 [31.0%]) were diagnosed before age 50 years (**Table 1**), and the cohort was predominantly white (1376 [80.5%]). The vast majority of patients in the cohort were diagnosed at an early stage, with half of the patients (737 [50.3%]) diagnosed at stage I and almost 90% of the patients (1316 [89.8%]) diagnosed at stage I or II. Less than 40% of patients (556 [38.0%]) were found to have positive lymph nodes at diagnosis, and two thirds of patients (970 [66.2%]) had small (T1) tumors. Patients were followed up for a median of 6.8 years after diagnosis, and 246 patients died of breast cancer.

Body weight at diagnosis was weakly associated with breast cancer death overall (**Table 2**). When restricted to patients with early-stage disease, however, we observed a statistically significant linear trend of increasing weight with increasing likelihood of dying of breast cancer. Compared with women with a body weight of 133 lb (60 kg) or less at diagnosis, women who weighed 175 lb (79 kg) or more experienced a greater than 2-fold increased risk of breast cancer death. We did not observe a linear increased risk of breast cancer death with increasing body weight among patients with higher-stage disease.

There was no evidence of interaction of ER status and body weight for all stages combined (**Table 3**), although the risk of dying of breast cancer was nearly 3.5 times higher for heavier women with ER-negative can-

Table 2. Association of Body Weight and Breast Cancer Death Overall and by Stage*

	Alive or Died of Other Cause	Died of Breast Cancer	Hazard Rate Ratio†	95% Confidence Interval	P Value
Weight, lb					
All stages					
<133	305	46	1.00		
133-150	296	55	1.78	1.09-2.89	
151-174	273	52	1.41	0.86-2.29	
≥175	277	72	1.60	0.99-2.56	.14
Stage I, IIA					
<133	258	16	1.00		
133-150	256	18	1.26	0.47-3.08	
151-174	223	18	1.73	0.72-4.20	
≥175	231	26	2.39	1.01-5.63	.03
Stage IIB-IV					
<133	44	30	1.00		
133-150	40	37	2.13	1.20-3.79	
151-174	49	34	1.31	0.73-2.36	
≥175	46	46	1.34	0.76-2.38	.73

*Values are expressed as number of patients unless otherwise indicated.
†Multivariate models included age, grade, stage, tumor size, lymph node status, and estrogen-receptor status.

Table 3. Interaction of Body Weight and Estrogen-Receptor (ER) Status With Breast Cancer Death Overall and by Stage*

	Alive or Died of Other Cause	Died of Breast Cancer	Hazard Rate Ratio†	95% Confidence Interval	P Value for Interaction
All stages, weight, lb					
ER status					
Positive					
<151	433	54	1.00		
≥151	402	62	1.48	0.93-2.34	
Negative					
<151	168	47	2.43	1.45-4.06	
≥151	148	62	3.47	2.11-5.71	.92
Stage I, IIA					
ER status					
Positive					
<151	375	22	1.00		
≥151	338	19	1.16	0.51-2.62	
Negative					
<151	139	12	1.56	0.58-4.18	
≥151	116	25	4.99	2.17-11.48	.10
Stages IIB-IV					
ER status					
Positive					
<151	57	32	1.00		
≥151	63	43	1.28	0.73-2.25	
Negative					
<151	27	35	2.37	1.29-4.37	
≥151	32	37	1.93	1.05-3.53	.25

*Values are expressed as number of patients unless otherwise indicated.
†Multivariate models included age, grade, stage, tumor size, lymph node status, and ER status.

cers compared with thinner women with ER-positive cancers. Among women with early-stage disease (I and IIA), however, there was weak evidence of interaction of ER

status with body weight in which the increased risk of dying of breast cancer for heavier compared with thinner women was greater for women with ER-negative than with ER-positive cancers. We observed a 3-fold increased risk of breast cancer death among heavier compared with thinner women with ER-negative tumors, compared with only a slightly increased risk of breast cancer death among heavier compared with thinner women with ER-positive tumors. Among women with higher-stage disease (IIB-IV), risk of breast cancer death was increased for women with ER-negative cancers regardless of body weight at diagnosis.

We also examined the association of BMI with breast cancer mortality, and we examined whether there was an interaction of BMI with ER status (results not shown). The results for the association of BMI with breast cancer mortality were slightly attenuated overall and by stage. Among women diagnosed with early-stage (I or IIA) breast cancer, women in the highest quartile of BMI compared with those in the lowest quartile experienced an HR ratio of 1.88 (95% CI, 0.75-4.70) (trend $P = .09$), somewhat attenuated compared with the findings for body weight. However, the results of the interaction of BMI and ER status were nearly identical to those observed for weight and ER status, overall and by early- and late-stage disease (not shown).

We examined whether chemotherapy use for the primary treatment of breast cancer varied across body weight categories. We observed that the proportion of patients receiving chemotherapy was nearly equally distributed across weight categories for all stages combined ($\chi^2 P = .80$ for a difference in proportions across weight categories) and for early- ($\chi^2 P = .82$) and late-stage ($\chi^2 P = .84$) disease separately. We also observed no material difference in any of the HR ratios when the multivariate models included chemotherapy.

COMMENT

Correcting for known risk factors for breast cancer mortality, we found a statistically significant, dose-response relationship between weight at the time of breast cancer diagnosis and breast cancer mortality in early-stage (I and IIA) disease, with increasing weight associated with decreasing disease-specific survival. Women with early-stage breast cancer in the highest quartile of weight in our study had a nearly 2.5-fold increased risk of dying of breast cancer compared with women in the lowest quartile of weight. Women in our study with early-stage, ER-negative disease and weight higher than the median experienced a 5-fold higher likelihood of dying of breast cancer than women in the lower half of the weight range with ER-positive tumors.

Our findings corroborate the preponderance of evidence that suggests that obesity at diagnosis negatively affects breast cancer survival.^{2,3} More than 50 studies have examined the relation of body size and breast cancer survival, and most have noted an increasing likelihood of breast cancer death with increasing body size.¹ Several prior studies corroborate our study's finding of the association of body size with breast cancer death that is most striking among women with early-stage disease.⁴⁻⁸

We also noted weak evidence of an interaction of weight and ER status with breast cancer mortality, with a greater increased risk of breast cancer death among heavier patients with early-stage, ER-negative breast cancer than we observed for those with ER-positive disease. Our findings for ER-negative cancer contrast with the results of the few previous studies that have examined this association. In a large Norwegian cohort, the investigators reported a direct association of body size and breast cancer mortality among women with ER-positive tumors and an inverse association among women with ER-negative tumors.⁹ An important difference between the current study and the Norwegian study was the timing of collection of body-size data relative to breast cancer diagnosis. In the earlier study, body size was ascertained an average of 12.5 years before breast cancer diagnosis, whereas in the current study, body size was ascertained at diagnosis. Body size more than a decade before diagnosis may be a poor proxy of body size at diagnosis, especially in a cohort that included young women. The reference group likely included women who had gained weight in the years leading up to diagnosis and the higher weight categories probably included women who had lost weight in the years leading up to the diagnosis, making interpretation of the findings tenuous. A recent review of data from a large, randomized, prospective treatment trial involving more than 3000 women with early-stage breast cancer found no relationship between obesity (BMI ≥ 30) and breast cancer-specific survival in women with ER-positive breast cancer.¹⁰ Interestingly, however, the obese women in this trial experienced a higher incidence of new breast cancers and other nonbreast cancers and a higher risk of mortality from diseases not related to breast cancer than women in lower weight ranges.

It is possible that the mechanisms postulated to underlie the association of obesity with increased breast cancer risk may also underlie the association of obesity with increased breast cancer mortality. It is postulated that the association of body size and breast cancer risk is mediated by relation of body size with bioavailable plasma steroid hormone levels.¹ The C19 steroid androstenedione is converted to estrone in adipose tissue via the aromatase enzyme complex, and the estrone is then available for conversion to the biologically potent estradiol, the major form of estrogen produced by postmenopausal women.^{11,12} The increased risk of death in this study was mainly restricted to women with ER-negative cancers. Whether increases in bioavailable estrogen due to increased body fat are important mechanisms in ER-negative cancers is unclear. However, recent work has also focused on other potential mechanisms that may affect breast cancer survival such as insulin, insulin-like growth factor, and leptin, a neuroendocrine hormone produced almost exclusively in adipose tissue.¹³ Insulin, insulin-like growth factor, and leptin, hormones found in higher levels in the blood of obese women,^{14,15} have been reported to potentiate the effects of circulating estrogens in promoting breast cancer cell proliferation and angiogenic activity.¹⁶ Insulin and insulin-like growth factor exert their effect by reducing circulating levels of sex hormone-related binding globulin, thus increasing circulating estrone and estradiol levels.¹⁷ Leptin has a di-

rect effect on breast cancer cell epithelial proliferation and angiogenic activity and an indirect effect by inducing aromatase activity in the fat cell, promoting estrone and estradiol production.¹⁸

As with any study, our study had certain limitations. We obtained body weight at diagnosis, which could have been affected by the disease process. However, anecdotal and observational evidence suggest that women with breast cancer tend not to lose weight as a result of the disease process, at least in the early stages, and they often gain weight during systemic adjuvant therapy.¹ Therefore, it is unlikely that collecting body weight information at diagnosis markedly biased our results. We did not collect information on weight change after diagnosis, and it is unclear whether weight at diagnosis or weight change after diagnosis separately influence breast cancer prognosis. Weight gain after breast cancer diagnosis and treatment is a commonly observed and real phenomenon¹⁹ that does not appear to be due to any known metabolic effect of adjuvant chemotherapy.²⁰ It is possible that weight gain after the diagnosis and treatment of breast cancer would be associated with a worse prognosis than weight maintenance or loss as reported in 1 study.²¹ This is an interesting area for further investigation in this cohort.

We were unable to obtain medical records for all patients in the study, and it is possible that factors associated with having missing medical records could have also been related to body size or breast cancer outcome. However, patients with missing medical records did not differ by stage ($\chi^2 P = .62$), the strongest prognostic factor, from patients with completed medical record abstractions, and the proportion of patients with missing medical records was extremely low (4%), making it highly unlikely that the missing data could have materially affected the findings. Similarly, we were unable to obtain ER status from either the medical record or the laboratory analyses for some of the patients. The patients with missing tumor ER status were more likely to have been diagnosed with earlier-stage disease ($\chi^2 P < .001$) than patients with known ER status, because patients with very early-stage disease often have tumors with insufficient tissue to perform ER studies. However, the proportion of patients with missing ER status was very low (6%), again rendering it highly unlikely that the missing data would have materially affected the results.

We have shown that increased body weight at the time of diagnosis of breast cancer is a risk factor for poorer survival in early-stage breast cancer. Chlebowski et al²² have recently reviewed the evidence and rationale for weight loss as part of patient management after the diagnosis of breast cancer. Body weight is a function of multiple factors, some of which are potentially modifiable, including increased energy intake, decreased energy expenditure,²³ and depressive symptoms.²⁴ The National Institutes of Health, Bethesda, Md, has published clinical guidelines²⁵ for the identification and treatment of overweight and obesity in adults that incorporate all 3 modifiable factors: dietary modification, physical activity, and behavioral intervention with ongoing contact. Unfortunately, there is no current prospective clinical trial of weight reduction or control in patients with breast cancer incorporating the comprehensive, multifactorial ap-

proach recommended in the National Institutes of Health clinical guidelines. At least 2 prospective studies of dietary modification in patients with breast cancer are studying the effects of healthy diets on survival in women with early-stage breast cancer,^{26,27} but neither is targeting overweight women and neither is primarily concerned with weight control or loss. There is substantial evidence suggesting that physical activity is associated with a reduced risk of developing breast cancer,^{1,28} and at least 1 randomized trial of supervised exercise in women with early-stage breast cancer has demonstrated functional benefit (less fatigue and better sleep). However, only 1 subset of patients actually lost weight, and there are no survival data as yet.²⁹ Understanding why obese women have a higher breast cancer incidence and poorer survival can and should lead to more effective breast cancer prevention and treatment interventions, which may, in turn, require carefully designed, large-scale studies to determine benefit.

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DISCUSSION

Theodore X. O'Connell, MD, Los Angeles, Calif: Obesity has reached epidemic proportions in the United States. We all know the multiple negative effects of obesity on health including increased risk of heart disease, hypertension, diabetes, arthritis, etc. We have also known for more than 30 years that there is an increased risk of breast and endometrial cancer in obese women. The etiology is thought to be due to increased estrogen levels in patients that are overweight. In this presentation, we are told that obesity may not only increase the incidence of breast cancer but may also adversely impact prognosis and survival.

Given that we are talking about obesity and its effect on breast cancer, we first must question whether this is what is really presented here today. Obesity was not measured by such accepted methods as a body mass index (BMI) but simply rather with increasing body weight. Obviously this may not be defined as obesity since a patient who is 150 lbs and 4' 10" may be obese by standard measures, but one that is 6' tall and 150

lbs may not be in the obese range by BMI. I ask the authors why body mass index or other measures of obesity were not done to determine if obesity itself rather than increasing body weight had the negative impact on survival.

The paper also states that prognosis is worse in patients with estrogen receptor–negative tumors than in patients with estrogen receptor–positive cancers. This fact is already very well known and accepted for many years. It is thought that estrogen-binding, negative tumors are less differentiated, are more aggressive, have a higher incidence of visceral metastases, and do not respond to hormonal agents, all of which are reflected in the poorer prognosis. In this paper, the largest hazards ratio difference is between the ER-positive [estrogen receptor–positive] patients of normal weight compared with the ER-negative patients greater than 150 lbs (1 vs 4.99), but how much of this difference is due to the difference in tumor biology as defined by the presence or absence of estrogen receptors and how much due to influence of the increased weight?

The negative influence of increasing body weight is not so marked in the ER-positive patients (hazard ratio, 1 vs 1.16) but rather in the ER negatives (hazard ratio, 1.56 vs 4.99). This presentation is really a subgroup analysis, correlating prognosis with a large number of variables and subgroups until a positive correlation develops such as left-handed women wearing red shoes. In any subgroup analysis, we are always left with the question whether the correlation is real (a cause-effect relationship) or coincidence in which the subgroup has other undetermined risk factors that are actually producing the positive correlation. So is increasing weight and poorer prognosis a true correlation, and if it is, what are the reasons for it? The first question is why does the correlation not exist with the stage IIB patients or when the stage IIB patients are combined with the stage I and IIA patients? This is truly a very specific subgroup.

There are several possibilities for the negative effect on prognosis noted:

1. Obviously, all the patients who died had residual disease that was not apparent at the time of primary treatment. Staging is in reality a surrogate for identifying those with residual microscopic disease (ie, occult stage IV disease). We are really not concerned about those patients who are truly stage I or II and cured by the primary treatment but rather how many of these patients have microscopic residual disease and will need additional adjuvant therapy or will finally succumb to their disease. In the staging of all tumors, the incidence of occult residual disease increases from stage to stage and that is the value of the staging system. The question therefore is whether there was a higher proportion of patients with stage IIA disease in the overweight patients compared to those less than 150 lbs. A relative difference in percentages of patients with stage I and IIA among the various weight groups may explain the effects seen. Is the proportion of stage I and IIA patients the same in all the weight groups? The next question regarding staging is the element of misstaging. It is well known that patients with central or medial lesion staged only by axillary dissection are understaged with approximately 6% to 7% of patients being called stage I when they actually have internal mammary nodal disease and are actually stage II. In your study, did your heavier patients have an increased incidence of medial or central lesions and be possibly misstaged?

2. The second cause for this observed poorer prognosis is that these heavier patients actually have more aggressive disease. Other studies have shown that there is an increased preponderance of ER-positive tumors in obese patients. This is thought to be due to the increased levels of estrogen in these individuals stimulating microscopic subclinical ER-positive tumors to grow and become obvious clinical cancers. However, in ER-positive and ER-negative tumors, there is a continuum of posi-

tivity and negativity with the associated effects on prognosis. That is to say that not all ER tumors are equally responsive to estrogens with excellent outcomes or that all ER negatives have the same level of estrogen indifference and equally poor prognosis. The question is, does the hyperestrogenation in the overweight patient push tumors toward ER positivity so that even those with few ER-positive receptors are stimulated to grow and are diagnosed as an ER-positive tumor, leaving behind only the most ER negative and therefore the most aggressive? Is this a reversed Will Rodgers effect? Is there an unknown intrinsic difference in the ER-negative tumors between the normal weight and heavier patients? Or are there some other intrinsic factors in the heavier patient that stimulates a more aggressive behavior such as increased insulin, leptin, or other hormonal factors that are known to be elevated in obese patients?

3. The other factor that may have an impact on the poor prognosis seen in heavier patients is the use of adjuvant therapy. We know that adjuvant hormonal and/or chemotherapy has a positive effect on prognosis and survival in almost all groups of patients with breast cancer. Did patients who were heavier have a decreased use of adjuvant therapy than those who were of a lesser weight? Also, was the same type of chemotherapy used in the lighter vs the heavier patients? Could there be an effect of inadequate dosing in the heavier patients so that they do not get the same level of circulating chemotherapy as the lighter patients, or could the increased adipose tissue lead to sequestration of the active chemotherapy making it less effective?

This is a very interesting paper, which stimulates a great deal of thought. I know you don't have the answers to all the questions, but I would certainly appreciate your comments. I enjoyed listening to the presentation and look forward to follow-up studies on the etiologies of the outcomes presented.

Laura Esserman, MD, San Francisco, Calif: This is a very interesting paper and a very interesting discussion, and I would agree with many of the points that were raised. I think certainly that looking at mortality as an outcome can be confounding because you are combining both prognostic factors as well as response to treatment. We know certainly in the neoadjuvant chemotherapy setting that someone who has a locally advanced cancer, if they have a great response to therapy, will have the same outcome as someone with stage I, a 90% survival. So it is certainly possible that increased body weight is associated with an increase in the incidence of ER-positive breast cancer but tamoxifen treatment or some kind of hormonal therapy can mask any impact on mortality. To better tease out the association between incidence and mortality, it would be interesting to compare the incidence in these patients, stratified by body weight. That is possible to measure in your dataset and would contribute to our understanding of how weight affects breast cancer incidence as well as mortality.

I also thought the point about insulin growth factor [IGF-I] receptors or some of the other factors that are associated with overweight patients may be very important and operative in this setting because we know that IGF-I is a receptor for breast cancer and plays a role in stimulating growth. In light of the last paper, I think the question was asked, can we use this information to help us with differentiating prevention strategies? What is interesting about this data is that it suggests that weight affects not just ER-positive patients, which we might have thought previously, but maybe ER-positive as well as the ER-negative patients. I would encourage the authors to look at incidence of mortality and report the reports based on ER and PR results as well as IGF-I.

Christian de Virgilio, MD, Los Angeles: I enjoyed the paper, but I have some questions regarding the methodology. I noticed that you used mortality and body weight as the main outcome measures. How did you decide to put body weight as an out-

come measure? Also, in the univariate analysis, it did not appear that body weight was 1 of the factors associated with mortality, yet you then inserted body weight as a factor in the subsequent subanalysis. How did you decide to do that, and how did you arrive at the specific body-weight cutoffs? Did you use, for instance, decision-tree analysis or other statistical methodology?

Nathalie M. Johnson, MD, Portland, Ore: I also found this paper very interesting, and it raises lots of questions. I agree with many of the comments and questions already raised and want to ask a few more questions and challenge the authors to look further. First, I think the body mass index is really an important point. Secondly, is this really obesity or does it have more to do with diet and exercise? I think we all know that the American Cancer Society promotes 5 fruits and vegetables a day, and I think people who actually eat 5 fruits and vegetables a day probably have a lower body weight index. There has been some question about diet and exercise and association with breast cancer. So I challenge you to do a prospective study looking at those questions and asking patients questions on dieting and exercise habits. In addition, I would urge the authors to do the hormonal studies, not only estradiol, estrone, LH [luteinizing hormone], FSH [follicle-stimulating hormone], and DHEA [dehydroepiandrosterone] sulfate, which Rod Pommier has been looking at, which I think is interesting, but also the insulin growth factors and so forth. I think it would be a very fascinating study, and I look forward to hearing more from you in the future.

Lawrence D. Wagman, MD, Duarte, Calif: I would like to thank Dr Greif. He gave me a copy of the manuscript ahead of time, and Dr O'Connell hit most of the points that I was thinking of also. I guess that means that I have been paying attention to him for many years. In any event, I would like to punch a couple more. I knew that Dr O'Connell would be bringing up much of the scientific concern, so I thought a little bit about the social elements. I was wondering if there is some element of this obesity bias against patients being fully treated, similar to what we see in the workplace and may also be seeing in medical care. He brought that up, and I was just thinking of ways and decision making, even in the stage I group or the early breast cancer, which indicates node negative stage IIA. In our practice, nearly all of these patients would be treated with cytotoxic chemotherapy. And particularly since they are relying on the cytotoxic chemotherapy for their modest but real improvement in survival, any delay in that, whether it is because of venous access or because of some bias in delivering it, I think becomes critically important.

I think the study really gives Dr Greif and colleagues an opportunity to look at a unique question because the ER-negative, lower-body weight patients do worse than the higher-body weight patients. There is the differentiation that you might look at for the nonsocial issues.

Another point was left partially said but not completely queried. There are genes related to obesity, and the difference is in the metabolism. We know from PET [positron emission tomography] scanning that tumors are glucose metabolizers, and it seems to me that there might be something specifically to look at in microarray analyses, looking specifically at enzymatic processes that go on in these tumor cells. Then the difference in patients who are obese vs nonobese or of greater body weight vs lesser body weight would not be because of any issues related to what they eat or where they live but just simply the metabolic processes that affect both their normal and cancerous cells.

Dr Greif: I want to thank all of the discussants and particularly Dr O'Connell for his very thoughtful and insightful and probing questions. I think they are excellent questions, and they are questions that we asked also.

Several of the discussants asked questions about body weight vs BMI—Dr Johnson, Dr de Virgilio, and also Dr

O'Connell. There are currently more than 50 studies in the literature that I could find that look at body weight and breast cancer risk, and a handful of others that look at body weight and breast cancer survival. The majority use body weight. And I can tell you why, having done one of these studies. The reason is that it is difficult to get height information, retrospectively, and have a decent number of cases. Nonetheless, some have put forward very elaborate arguments as to why they used weight over body mass index, including that as people get older and their bone density goes down, their body weight obviously has a much more important effect on their BMI and therefore BMI is less accurate. I don't agree with that. It is largely because weight is more readily available.

Dr O'Connell and Dr Wagman pointed out that the ER-negative patients who are in the lesser weight category had a worse prognosis than the ER-positive patients with either lower or higher weights, and there is no question about that. One of the conclusions in our manuscript is that ER status is a very important factor in breast cancer survival. The important point was that there was a linear relationship between weight and survival in each of the categories, and I think that is very real.

I wanted to address the issue of occult residual disease, which Dr O'Connell raised, because I think that is very important, and I think what is going on here has to do with the amazing fact that the body fat is an efficient endocrine organ and what is going on in the patient's body fat is that the C19 steroid androstenedione is being converted to estrone by the aromatase enzyme system. That has been very well described, and then the estrone is available for conversion to the potent form of estradiol. And there is a direct relationship between body weight and estradiol levels in postmenopausal women.

Further, as was pointed out by several of the discussants, there are other hormones that are acting in this system and at an increased rate in overweight and obese women. Insulin, insulin-like growth factor, and leptin, which is a neuroendocrine substance, which is also found in higher levels in obese women, all act either directly or indirectly on breast cancer cells, causing breast cancer cell proliferation and angiogenic activity.

And I think that Dr O'Connell is absolutely right. All of these women may have residual disease, but the overweight and obese women may have these factors driving breast cancer cell proliferation and resulting in worse outcomes.

The other thing that I wanted to point out is what Dr Johnson alluded to in her question and that is that we need to do some translational research here. We need to take this research and make it useful. There are currently at least 2 prospective studies of dietary modification in patients with early-stage breast cancer that are ongoing, but neither is targeting overweight women and neither is primarily concerned with weight gain or loss. There is evidence that physical activity is associated with decreased risk of developing breast cancer and at least 1 trial is looking at supervised exercise in women with early-stage breast cancer.

I submit to you that it is probably reasonable at this stage to recommend to women with a new diagnosis of breast cancer if they are overweight to lose weight and if they are not overweight to keep their weight at that level. I have been referring our patients to our special program. It's called The Positive Choice Program, which uses the NIH [National Institutes of Health] recommended 3-prong approach: decreased energy intake, which is diet; increased energy expenditure, which is exercise; and behavior modification with appropriate follow-up to see that women are actually losing weight and/or maintaining weight. Given the magnitude of risk that obesity presents, such a program may have as much of an impact on survival in women with early-stage disease as adjuvant or chemotherapy or hormonal therapy, not to mention the associated decrease in comorbid events and new cancers.