Obesity, Guideline-Concordant Treatment, and Mortality in Patients with Locoregional Invasive Breast Cancer

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ABSTRACT

Purpose: Although treatment advances have substantially reduced mortality among the population of affected women as a whole, mortality after a diagnosis of invasive breast cancer has been observed to be higher among women who are obese. Given the large number of women diagnosed each year and the increasing proportion of these women who are obese, characterizing this disparity and addressing potential mechanisms behind this disparity is a significant public health concern. We examined the relationships between body mass index (BMI), cancer treatments received, and all-cause or breast cancer-specific mortality in order to test the hypothesis that the likelihood of treatment concordant with National Comprehensive Cancer Network (NCCN) clinical practice guidelines could be a mediator in the relationship between BMI and all-cause or breast cancer mortality among women with locoregional invasive breast cancer.

Methods: Women diagnosed in 2004 with Stage I, II, or III breast cancer (n = 5,400) were identified from a population-based, National Program of Cancer Registries-funded Patterns of Care study. Differences in overall and breast cancer-specific mortality were investigated using proportional hazards regression models. Differences in treatment according to BMI category were investigated using adjusted logistic regression models. Finally, the hypothesis that treatment might mediate the relationship between BMI and mortality outcomes was tested by comparing proportional hazards regression models accounting for, and not accounting for, receipt of guideline-concordant treatment.

Results: Body mass index was inversely associated with overall mortality (HR for 5 kg/m^2 difference in BMI = 0.93, 95% CI, 0.87 – 0.95; p-value for trend = 0.02), although this

relationship was significant only in women aged 70 or older. Body mass index was not associated with breast cancer mortality in the sample as a whole, but among women with Stage I disease, women in the highest category of BMI had significantly higher mortality (HR for BMI ≥ 35 kg/m^2 versus the reference category = 4.74, 95% CI 1.78 to 12.59; p-value for trend = 0.004). Higher BMI was associated with greater odds of receiving overall guideline-concordant therapy, defined as treatment guideline-concordant in all domains of post-surgical therapy (p-value for trend = 0.01; OR for 5 kg/m2 difference in BMI = 1.09, 95% CI 1.02 to 1.15). BMI category was not associated with guideline-concordant therapy in any specific treatment domain, except among certain sub-groups. Receipt of guideline-concordant treatment was independently associated with lower overall mortality and lower breast cancer mortality; however, addition of the variable indicating guideline treatment receipt to proportional hazards models did not substantially alter point estimates of hazard ratios for overall mortality or breast cancer mortality.

Conclusion:

This examination of patterns of care and mortality among women with invasive breast cancer resulted in several findings that were contrary to hypotheses advanced at the outset of the study. Higher body mass index was associated with greater hazard for breast cancer mortality only among women with Stage I disease, was not associated with overall mortality among younger women, and was actually inversely associated with overall mortality hazard among older women over age 70. Higher BMI was associated with greater odds of receiving overall guideline-concordant therapy, defined as treatment guideline-concordant in all domains of post-surgical therapy. Guideline-concordant treatment also did not appear to be a mediator in the relationship between BMI and mortality among women with breast cancer. Taken together, these findings

suggest that factors other than treatment are more important in the relationship between body size and breast cancer outcomes, although additional research investigating the treatment-related pathway is warranted.

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CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW

Although breast cancer treatment advances have substantially reduced mortality among the population of affected women as a whole, particularly among those whose cancer is detected at an earlier stage, persisting disparities in relative mortality have been found to remain between obese and non-obese patients. Given the large number of women diagnosed each year and the increasing proportion of these women who are obese, addressing potential mechanisms behind this disparity is important. Research has repeatedly documented obesity-related differences in overall and breast cancer mortality, but studies investigating potential mechanisms explaining these differences are fewer, particularly those focusing not solely on biological factors but systematically comparing attributes of patients' treatment with standardized practice guidelines intended to improve these outcomes.

Obesity and Disparities in Breast Cancer Outcomes

A substantial amount of evidence suggests not only that postmenopausal obese women are at greater risk for developing breast cancer than postmenopausal women who are not obese,[1] but also that breast cancer patients of all ages who are obese are likely to have a poorer prognosis with regard to disease recurrence and mortality.[2-31] The following discussion focuses on obesity and overall mortality as well as breast cancer-specific mortality.

Overall Mortality

Most studies examining the relationship between obesity and mortality in women diagnosed with breast cancer include overall mortality as a primary or secondary endpoint, and indeed it is

in some ways the most important outcome to consider when examining any potential risk factor. Therefore, while examining overall mortality is potentially less ideal for the purpose of assessing the role of treatment as a potential contributor to observed disparities, it is, along with quality of life, the ultimate relevant clinical outcome and therefore important to consider in this analysis.

A very substantial body of literature exists suggesting that higher body mass index (BMI) is associated with greater risk of death from any cause following a breast cancer diagnosis.[4-6,10,12,19,32,33] A recent meta-analysis showed that a majority of studies found a positive association between higher BMI and all-cause mortality after a breast cancer diagnosis, with a summary risk ratio (RR) of 1.25 for obese versus "normal" BMI at the time of diagnosis or shortly thereafter. In the same meta-analysis, pre-diagnosis BMI was even more strongly associated with all-cause mortality (summary RR = 1.41 for pre-diagnosis BMI in the obese category versus the "normal" category).[10] Some study findings do indicate that the association between obesity and overall mortality after breast cancer may differ according to patient characteristics, and may not be present at all in some subgroups. These include findings by Berclaz et al that the association between BMI and all-cause mortality was significant only among premenopausal women,[4] as well as findings by Kwan et al that higher BMI was associated with overall mortality after breast cancer only among certain racial/ethnic categories.[33] Kamineni et al found that among women diagnosed with early-stage breast cancer following screening mammography, BMI reported within 2 years before diagnosis was not significantly associated with all-cause mortality.[17] Multiple groups of authors found that obesity was not significantly associated with mortality in women with triple hormone receptor-negative breast cancer,[34-36] although this is a high-risk group in which a ceiling effect may have been present. It is also important to note that many

studies linking BMI and mortality after a breast cancer diagnosis do not describe a completely linear trend, but rather a U-shaped curve, with underweight patients also at higher risk of death.[10] However, when taken as a whole, the existing literature strongly indicates that, potentially with the exception of those who are underweight, women with higher BMI at the time of diagnosis are at higher risk of all-cause mortality following a breast cancer diagnosis.

Breast Cancer-Specific Mortality

In addition to the observed relationship between higher BMI and overall mortality, a substantial amount of literature exists suggesting that higher BMI is related specifically to the risk of dying from breast cancer.[10,16,17,30,31,33] A recent meta-analysis showed a majority of studies finding a positive relationship between obesity and breast cancer death, with a pooled hazard ratio (HR) for breast cancer mortality of 1.33 compared to non-obese women.[30] Another meta-analysis showed a positive relationship of similar magnitude (HR = 1.26 for obese women compared to non-obese women).[31]

A smaller number of studies indicate, in contrast, that an association between obesity and breast cancer mortality is not present,[12,34,37-43] or may not be present among women in certain subgroups defined by menopausal status, tumor characteristics, or other characteristics. For example, Reeves et al found that the association between obesity and breast cancer mortality was present only among postmenopausal women,[44] and similarly, Eralp et al found no correlation between BMI and prognosis among women 35 years of age or younger at diagnosis.[45] These findings may be related to differences in the characteristics of breast tumors that tend to occur in younger women and those that occur in older women,[2] and suggest that future studies of breast

cancer survival according to BMI should consider a potential interaction with age or menopausal status. More recently, Kwan et al found that, within a California-based study population, higher BMI was associated with greater risk of breast cancer mortality among Latina women and non-Latina white women, but not among African-American and Asian-American women (although among the latter group, waist-to-hip ratio was predictive of breast cancer mortality).[33]

However, despite some variations in findings on the presence, universality, and magnitude of the association between BMI and increased breast cancer mortality, no studies have found a significant association between higher BMI and decreased disease-specific mortality, excluding a few subgroup analyses. These include Maehle and colleagues' findings that obesity was associated with higher breast cancer mortality in general, but was associated with lower breast cancer mortality for patients with estrogen and progesterone receptor-negative tumors.[46] Studies showing a null association or a very modest association between obesity and breast cancer prognosis are often secondary analyses of clinical trial data,[4,39,42,47,48] a tendency that has been speculatively attributed to several factors including more accurate staging, which allows investigators to better separate obesity from its correlate of later diagnosis, and protocol mandates for monitoring and adequate dosing.[30,49]

The observed pattern of higher breast cancer-specific mortality in obese patients likely reflects multiple factors. Before the proposed contributors to the relationship between obesity and death due to breast cancer are enumerated, it should be noted that at least a small part of the observed association may be due to statistical artifacts. Confounding by sociodemographic characteristics associated with obesity that also correlate with worse outcomes may be present and must be accounted for in any analysis attempting to identify causal contributors. In addition,

obesity is potentially related to systematic inaccuracies in tumor staging, as mentioned indirectly in the preceding paragraph. Obese women may be more likely to have their tumors staged lower than is actually the case, and while it is unlikely to explain very much of the observed association, it should be considered that this possibility could result in an inflated estimate of its strength.[50]

Several mechanisms by which obesity may actually be related to higher breast cancer mortality have been proposed. Of these, biological mechanisms have perhaps been the most thoroughly examined to date. Obesity is associated with multiple physiological risk factors for breast cancer mortality, including higher levels of endocrine factors related to adipose tissue that are thought to promote tumor progression directly and indirectly. In particular, estrogen and insulin pathways, both of which are altered in obese patients compared to non-obese patients, have been closely linked to tumor growth and survival, as well as to the migratory potential of breast cancer cells.[48,51,52] Chronically higher levels of inflammation, strongly associated with obesity, influence tumor growth through multiple mechanisms.[48,52] Proinflammatory cytokines present in elevated levels have been found to contribute to tumor progression directly, but chronic inflammation related to obesity may also contribute to differences in gene expression in adipose stem cells, making these cells more likely to act within the tumor microenvironment to promote tumor survival.[53] Differential production of adipokines, including leptin and adiponectin, may also be involved in causal pathways linking obesity and breast cancer mortality.[48,52] Obese individuals also tend to have lower levels of serum vitamin D, which has been found to be inversely associated with breast cancer mortality.[54]

In addition to these biological mechanisms, obese patients tend to have larger tumors at treatment onset due in part to delayed diagnosis.[48,55-57] Delays in breast cancer detection among obese women can result from differences in screening patterns.[55,58,59] In addition, technical challenges are frequently encountered when using available imaging technologies with women who have a larger body size, larger breasts, and/or more adipose tissue. These issues can not only increase the patient burden and time required for screening, but can also make these screening methods less effective in accurately detecting and characterizing tumors among obese women.[60]

Recognizing the multifactorial nature of the relationship between adiposity and breast cancer mortality, we hypothesized that in addition to influences such as biological factors and delayed diagnosis, differences in the care received once a tumor is diagnosed, a less-explored factor thus far, may also contribute to the disparity between obese and non-obese women in breast cancer outcomes.

Obesity and Breast Cancer Treatment Disparities

We hypothesized that differences in treatment may be a contributing factor to the pattern of poorer outcomes in obese breast cancer patients; that is, the difference in outcomes may be partially attributable to obese patients having a lower likelihood of receiving adequate treatment for their breast cancer.[30,49,61-63] Our hypothesis was motivated in part by previous findings regarding disparities in treatment related to body size among breast cancer patients.

Disparities in Treatment

Previous studies that have investigated the association between obesity and breast cancer treatment have most often focused on adjuvant chemotherapy, an important and broadly

recommended aspect of treatment.[64,65] Substantial variation in chemotherapy treatment has been found among patients who differ with regard to multiple demographic factors,[66-68] one of which, many investigators have found, is obesity. The majority of adjuvant chemotherapy studies that have examined dose intensity have found that reduced doses were commonly given to obese patients.[62,63,69-73] One 2004 study in which an association between BMI and higher mortality was observed also showed that even within a clinical trial setting, dose intensity reductions occurred very frequently.[4]

Studies focusing on patterns of care in adjuvant chemotherapy show that the dose reduction seen in the treatment of obese patients has occurred frequently, largely as a result of reluctance to deliver actual body weight-based doses on the part of physicians concerned about the consequences of large doses, in spite of evidence that giving doses based on actual, rather than "ideal" or "adjusted," body weight results in higher efficacy without higher incidence of toxicity-related adverse events.[62,69,74-77] Indeed, some studies have found that when chemotherapy is delivered at the appropriate dose intensity, patients of higher BMI have no worse prognosis compared to patients with lower BMI.[47,77] A 2012 report by an expert panel representing the American Society for Clinical Oncology (ASCO) concluded that the strength of the body of evidence supporting both the lack of excess toxicity or myelosuppression in obese patients dosed according to actual body weight, and the lower disease recurrence and mortality associated with this practice, was compelling with regard to most cancer types, including breast cancer. A recent ASCO clinical practice guideline was issued stating that full weight-based cytotoxic chemotherapy should be used to treat obese cancer patients except in the case of a few specific

chemotherapy agents.[78] As this guideline was issued in April 2012, the long-term impact on clinical practice and breast cancer outcomes has yet to be determined.

Other aspects of breast cancer therapy that have been the topic of investigation with regard to obesity include receipt of appropriate primary therapy and treatment with aromatase inhibitors (AIs). While little, if any, difference between obese and non-obese patients' treatment has been found to exist with regard to primary treatment,[79,80] some studies indicate that obese patients may have been receiving inadequate doses of AIs.[25,81] Continuing to examine the relation between obesity and patterns of care in breast cancer patients is important as a part of the effort to understand and reduce the increased risk of mortality among the obese breast cancer patient population.

Obesity and Adherence to Clinical Practice Guidelines for Oncology

There has been little research on the relation between obesity and patterns of care as measured against existing widely disseminated clinical guidelines,[79,82] and studies that have addressed the question of obesity and patterns of care using clinical guidelines as a metric for comparison have focused most frequently on one to two treatment modalities. Brewster et al examined receipt or no receipt of recommended or discretionary adjuvant chemotherapy; Buist et al examined primary surgical treatment as well as adjuvant chemotherapy.[79,82] Kimmick et al examined obesity and guideline concordance across multiple domains, though indirectly as part of an examination of comorbidities' effect on likelihood of guideline-concordant treatment.[83]

The use of adherence to clinical practice guidelines as a means of capturing variations in patterns of care has strengths and limitations. A substantial strength is the increasing relevance of

clinical guidelines. In research settings and elsewhere, there is a growing interest in the role of clinical guidelines in practice. Clinical guidelines have frequently been demonstrated to be effective at decreasing inappropriate variation in care and improving outcomes; in some settings, there is strong support for adherence to guidelines being explicitly considered a quality metric.[84] The National Comprehensive Cancer Network (NCCN) guidelines for breast cancer treatment in particular have been increasingly informed by patient advocate groups, improving the likelihood that they reflect patients' values as well as experts' judgment.[85,86] As interest in the role of clinical guidelines continues to develop, particularly regarding the use of guidelines in identifying and decreasing inappropriate variation in care,[87] study designs incorporating comparisons of specific aspects of patients' care to the applicable clinical guidelines may become more common.

However, an important consideration when interpreting the results of research in this area is that perfect compliance with guidelines is not necessarily a desirable outcome – there may be situations in which clinical factors not captured in guidelines would influence physicians and patients to make a decision not in line with the guidelines, and in the analysis of data these reasons may not be apparent. Thus, determining the "right" amount of adherence for any given group is difficult. In addition, sets of guidelines for specialty care are often numerous and may sometimes offer inconsistent conclusions.[88] Nevertheless, evidence-based clinical practice guidelines known to be disseminated, and used, widely and increasingly[87] can offer a standard for comparison of patients' treatment experiences.[66,89]

Guideline-Concordant Treatment and Disparities in Cancer Outcomes

Some research indicates that a substantial association exists between treatment not adhering to NCCN clinical guidelines and mortality in the contexts of ovarian cancer,[90-92] high-risk colon cancer,[84] gastric cancer,[93] and pancreatic cancer,[94] leading some authors to conclude that the NCCN guidelines are an appropriate means of comparing cancer care quality between treatment facilities.[84] Relatively little research, in particular recent research, has addressed the question of whether, and how much, guideline-concordant treatment is associated with improved survival among patients with locoregional breast cancer. Minter et al, using data on patients treated in 1991-1993, found that NCCN guideline adherence did not significantly affect mortality; however, this study was underpowered, with only 129 patients included.[95] Another older study by Hebert-Croteau et al found that adherence to a 1992 guideline set predicted survival among moderate- to high-risk breast cancer patients.[96] A few more recent studies have investigated this question,[97-100] three of which were conducted in Germany, using a national guideline set as a frame of reference.[97-99] Each of these German studies also showed a survival benefit associated with guideline adherence. (Two of these studies focused on high-risk patient groups; these studies also included data from a single group of university and partner clinics.[97,98]) Maskarinec and colleagues, in another recent study, found that adherence to the National Cancer Institute's Physicians Data Query (PDQ) was significantly associated with lower all-cause and breast cancer-specific mortality, a notable finding given the small sample size (382 women, all diagnosed in Honolulu, Hawaii).[100] These results should be considered in light of the possibility that some of the association between guideline-concordant treatment and higher survival may not be directly attributable to the impact of receiving recommended treatment, but rather a reflection

of better initial health predicting receipt of guideline therapies, particularly rigorous treatments that might be less tolerable by patients whose health (aside from the cancer) is less robust. However, the widely accepted theoretical foundation of the guidelines is that they do improve survival, and they represent evidence from clinical trials supporting the positive impact of the recommended treatment. Therefore, while patients with differing extent of disease may benefit differentially,[84] it is not unreasonable to expect that there is a true, and substantial, contribution of guideline-concordant treatment decisions to improved outcomes in cancer patients.

A small body of research, as discussed earlier, has focused on the association between BMI and mortality according to treatment-related factors; for example, the 1996 study by Rosner et al and the more recent 2014 study by Ladoire et al, both examining whether the BMI-mortality relationship was present among women receiving appropriately dosed chemotherapy. However, to our knowledge, there have been no studies specifically examining whether receipt or nonreceipt of NCCN guideline-concordant treatment mediates the relationship between BMI and mortality among women being treated for breast cancer.

Summary

The literature connecting obesity with higher overall and breast cancer-specific mortality is substantial and rich. However, only a small proportion of studies have examined treatment-related factors as a potential contributor to the mortality differential between obese and non-obese patients. To address this limitation, we compared overall and breast cancer mortality between women with higher and lower BMI in a study population consisting of women all diagnosed in the same year with locoregional disease, and within the same population, examined

variations in guideline-concordant treatment according to BMI in the domains of surgery, radiation therapy, and adjuvant systemic therapy. We subsequently connected these findings by considering how much, if any, of the association between BMI and overall or breast cancer mortality may be partially explained by differences in receipt of treatment adherent to guidelines.

CHAPTER TWO: SPECIFIC AIMS AND APPROACH

Aim 1 (Chapter 4): Compare overall and breast cancer specific mortality between women in this study population according to BMI category.

We hypothesized that:

1.1: Women in the highest BMI categories and women in the lowest BMI category would have higher overall mortality compared to women in the "normal" BMI category.

1.2: Women in the highest BMI categories would have higher breast cancer-specific mortality compared to women in the "normal" BMI category.

Aim 2 (Chapter 5): Examine whether obese patients are less likely to receive care that is consistent with recommended clinical practice guidelines than non-obese patients.

We hypothesized that:

2.1: Lymph node sampling and evaluation, as recommended in guidelines, would be less common among women in higher BMI categories compared to women in the "normal" BMI category.

2.2: Non-receipt of guideline-concordant radiation after surgery would be more common among women in higher BMI categories compared to women in the "normal" BMI category.

2.3: Non-receipt of guideline-concordant treatment within the modality of adjuvant chemotherapy would be more common among women in higher BMI categories compared to women in the "normal" BMI category.

2.4: Among those women whose treatment in the adjuvant chemotherapy domain was guideline-concordant, women in higher BMI categories would be more likely to receive a non-guideline-approved regimen.

2.5: Non-receipt of guideline-concordant treatment within the modality of hormonal therapy would be more common among women in higher BMI categories compared to women in the "normal" BMI category.

2.6: Failure to receive overall guideline-concordant treatment, defined as guideline concordance in all treatment domains addressed in the other hypotheses (radiation and the three systemic therapy components), would be more common among women in higher BMI categories compared to women in the "normal" BMI category.

Aim 3 (Chapter 6): Determine whether, and to what extent, receipt of guideline-concordant treatment mediates the relationship between BMI and breast cancer outcomes in this study population.

We hypothesized that:

3.1 (overall mortality): Non-receipt of guideline-concordant treatment acts as a partial mediator in the relationship between BMI and overall mortality.

3.2 (breast cancer mortality): Non-receipt of guideline-concordant treatment acts as a partial mediator in the relationship between BMI and breast cancer mortality.

To address these aims, we used the Breast and Prostate Cancer Data Quality and Patterns of Care study, supported by the CDC's National Program of Cancer Registries. This study includes data on individuals with breast cancer diagnosed in 2004 identified from population-based cancer registries in seven states.

CHAPTER THREE: STUDY DESIGN AND METHODS

Data Sources

The source of the data for this project was the National Program of Cancer Registries (NPCR) Breast and Prostate Cancer Data Quality and Patterns of Care (POC-BP) study, a population-based study focusing on patterns of care in initial (first course) treatment received by prostate cancer and female breast cancer patients in geographically diverse areas in the United States. In this study, breast cancer cases diagnosed in 2004 were identified from state tumor registries in Georgia, Louisiana, Kentucky, Minnesota, North Carolina and Wisconsin, and from two regional programs within the California Cancer Registry (the Los Angeles Cancer Surveillance Program and the Desert Sierra Cancer Surveillance Program). Cases were selected for inclusion using stratified random sampling based primarily on racial and ethnic characteristics, but also incorporating state-specific regional factors related to specific registry research goals, including Appalachian versus non-Appalachian region (North Carolina) and treatment facility type (Wisconsin).[101,102] Data routinely collected by these registries, including demographic, tumor-related, and basic treatment information, were augmented by abstraction or re-abstraction of medical records obtained from hospitals, free-standing treatment facilities, and individual physicians' offices and by linkages with census data. In addition, some information on adjuvant treatment and comorbidities was obtained directly from physicians and outpatient facilities.[101]

This data set was updated to include information on mortality for women identified in all tumor registries represented in the study. Women's vital status was determined through the linkage of cancer registry data with information from death certificates, as is routine for the

cancer registries; in addition, NPCR-supported use of the National Death Index enabled identification of deaths occurring in states other than the one in which a patient was diagnosed. Death certificate information including date and underlying cause of death was obtained for 2004-2009 for California, Georgia, Louisiana, Kentucky, Minnesota, North Carolina, and Wisconsin, and for 2004-2011 for at least some women identified through all registries except Wisconsin's (California registries collected data on a few additional women into 2012).

Analytic Data Set

The initial data set from the POC-BP study, described above, consisted of 9,142 women with first primary breast cancer diagnosed in 2004.

Inclusion and Exclusion Criteria

Women with a primary diagnosis of Stage I, Stage II, or Stage III breast cancer were chosen from the 9,142 included in the POC-BP data set. Women who did not receive any surgery for their cancer were excluded due to the possibility that some women may not have had surgery because of metastatic disease discovered after the initial characterization of their tumors for registry purposes. Finally, for the data set used in the main analyses, women with unknown height and/or weight were excluded. The final data set identified using these criteria consisted of 5,400 women (see Figure 1).

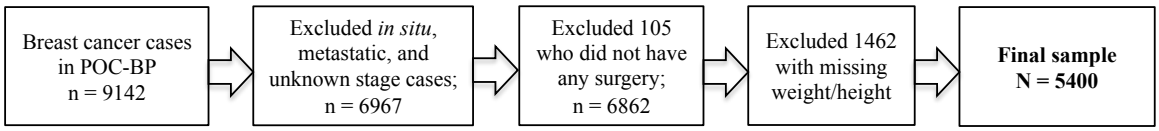


Figure 1. Formation of the study population for analysis.

The analytic data sets used in addressing each Aim were slightly smaller due to additional exclusion criteria. In the analyses for Aim 1, women with no available information on vital status

during the follow-up period (n = 6) were excluded. In analyses for Aim 2, women who had a second cancer diagnosis among their comorbid conditions (n = 39) were excluded. These women were excluded because some treatments for these other cancers, especially radiation therapy, could affect whether or not guidelines would recommend certain treatments for the breast cancer, and information about this other potential pre-2004 treatment history was not available. Analyses for Aim 3 excluded all women who were not included in Aim 1 analyses or Aim 2 analyses (n = 45).

Alternative analyses and sensitivity analyses were conducted to compare findings from these samples to those resulting from alternative approaches, including the use of a multiple imputation approach to allow inclusion of women otherwise eligible for inclusion in the data set who had unknown weight or height.

Conceptual Model

Figure 2, below, shows the conceptual model underlying our hypotheses. A more detailed conceptual model, including some posited factors or mechanisms beyond the scope of this analysis, is presented in Appendix A.

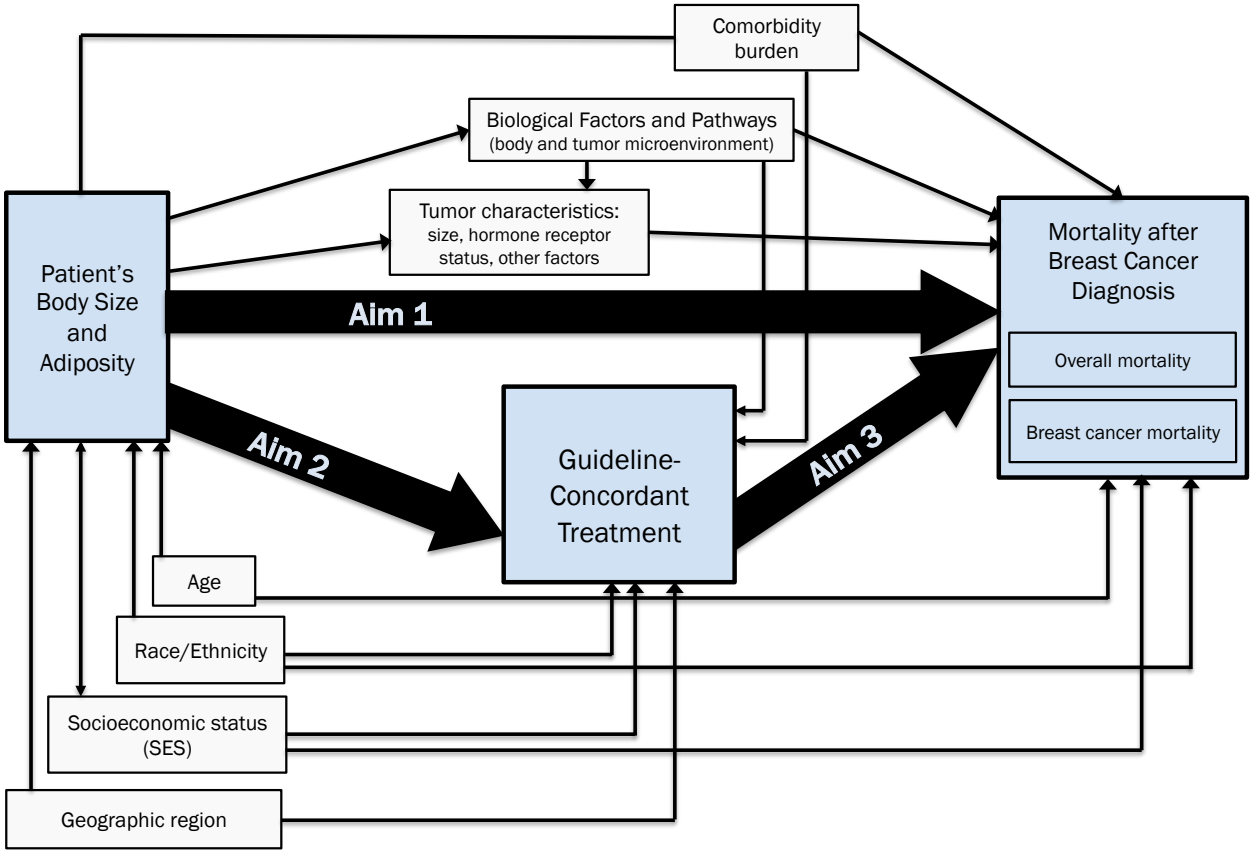


Figure 2. Conceptual Model Underlying Analysis of Aims 1, 2, and 3.

Statistical Analysis

Overview of Data Analysis

To address **Aim 1,** we used survey-weighted Cox proportional hazards regression models to examine whether overall mortality or breast cancer mortality differed according to BMI category in this study population. These models adjusted for demographic and clinical characteristics known or suspected to affect mortality after breast cancer diagnosis and treatment. We conducted stage-specific analyses and also tested whether interactions might exist between BMI and age at diagnosis, tumor registry (geographic area), or race/ethnicity. For **Aim 2**, we compared treatment of patients across BMI categories in a cross-sectional analysis, using logistic regression models adjusting for demographic and clinical characteristics to produce odds ratios (OR) and 95%

confidence intervals (CI) for receipt of guideline-concordant therapy within specific treatment domains, and then for overall guideline-concordant treatment, according to BMI. Models were stratified according to the POC-BP stratification criteria, used sampling weights to account for the POC-BP study design, and incorporated clustering by treatment facility using robust standard errors accounting for the number of cases treated at each treatment center. In addition to assessing whether BMI was related to receipt or nonreceipt of guideline-concordant treatment, we examined whether a patient's BMI might be related specifically to under-treatment or over-treatment in the domains of systemic adjuvant therapy (chemotherapy and hormonal therapy), conducted stage-specific analyses, and also tested whether interactions might exist between BMI and age at diagnosis, tumor registry (geographic area), or race/ethnicity. We addressed **Aim 3** using Cox proportional hazards models similar to those described in Aim 1. To test the hypothesis that mediation is present, we assessed whether adding a variable for overall guideline concordance attenuated the point estimate for the effect of BMI on mortality in each of these models.

Analyses addressing Aims 1 and 3 used time-to-event data, with overall mortality and breast cancer mortality being the endpoints. As described in the Dependent Variables section below, some women were followed longer than others due primarily to the fact that not all tumor collected data on vital status for longer than the protocol-specified 5-year period; thus, the time of vital status collection ranged from 5 years to 11 years. Vital status data beyond 8 years past the time of diagnosis (2012) were available for a very small number of women (fewer than 10), so all observations were censored at 8 years in survival analyses to avoid any undue influence. We considered that this difference in the amount of person-time contributed by women according to the tumor registry through which they were identified was unlikely to bias our

results because tumor registry is accounted for in the model design. However, to further address the possibility that this would be an issue, we conducted sensitivity analyses in which all women's vital status was censored at 5 years; results were almost identical to those including all available follow-up time (Appendix C, Table C5).

We conducted additional sensitivity analyses using the models for Aim 1 to address some potential data issues and to gain a more nuanced understanding of potential relationships between BMI, other factors, and mortality after a breast cancer diagnosis. One key issue was missing data. In order to address the substantial percentage of women from the parent data set for whom information on weight and/or height was missing, we first conducted analyses using body weight instead of BMI, which allowed us to take advantage of data from 40% of the 1462 women who were excluded in the main analyses; and then conducted a multiple imputation approach, in which BMI was calculated based on imputed weight or height among women with missing data for one or both of these variables.

We also recognized that the commonly used BMI categories reflect arbitrary cutoffs, and there may be other ways of grouping BMI values that would be more informative – that is, more predictive of the specific outcomes of interest in our analyses. We therefore conducted two different sensitivity analyses to explore possibilities for better characterizing the association between BMI and the outcomes examined. Spline-based models were used to decouple weight and height in the description of this association, as well as to allow for a data-driven non-linear model of the relationship. Additionally, we explored the use of regression trees to identify (a) whether BMI was a significant contributor in determining mortality and (b) what the most informative cutoff, or cutoffs, might be. A more detailed description of the design and results of these sensitivity analyses can be found in Appendix C.

In sensitivity analyses conducted for Aim 2, we compared findings from models using the definitions of guideline concordant treatment described below with alternative definitions. These sensitivity analyses are also described in greater detail in Appendix D.

Variables

Dependent Variables: Aim 1

Overall mortality

Time to death was defined as days between diagnosis and death. Complete data on vital status were available for women identified in each of the registries through the end of 2009, at least 5 years from date of diagnosis for all women. The Wisconsin registry, through which 9% of women were identified, did not collect vital status data on women beyond 2009, whereas other registries collected data up through 2011 (Georgia [24% of women], Louisiana [18%], Kentucky [6%], Minnesota [11%], North Carolina [11%]) or 2012 (California [21%]), constituting a 7- to 8-year follow up period. Follow-up vital status data were available for 20% of women at 8 years post-diagnosis, with the remainder censored prior to 8 years. Table 1 shows a year-by-year summary of women's vital status over time.

Table 1. Vital Status of Stage I-III Breast Cancer Patients Over Time.

Years since Diagnosis	Deceased		Alive		Censored at Date Last Known Alive	
	n	%	n	%	n	%
1	79	1.5	5315	98.5		
2	262	4.9	5132	95.1		
3	442	8.2	4952	91.8		
4	600	11.1	4794	88.9		
5	764	14.2	4630	85.8		
6	913	16.9	3052	56.6	1429	26.5
7	1009	18.7	1040	19.3	3345	62.0
8	1033	19.2	5	0.1	4356	80.8
9	1036	19.2	1	0.0	4357	80.8
10	1036	19.2	1	0.0	4357	80.8
11	1037	19.2			4357	80.8

Breast cancer-specific mortality

Time to death from breast cancer was defined as days between diagnosis and breast cancer-specific death, which was determined using cause-of-death data, in the form of ICD-10 codes. ICD-10 code C509 indicates that the primary cause of death was invasive breast cancer. Secondary cause of death was not identified in the POC-BP data set.

Dependent Variables: Aim 2

Guideline concordant care was identified based on NCCN Guidelines in Oncology, a widely disseminated guideline set providing detailed evidence-based recommendations for the numerous sequential decisions related to disease staging, management, and interventions in breast cancer. The NCCN guidelines are updated annually or biennially to provide up-to-date guidance based on available evidence. We compared women's treatment to NCCN guidelines version 1.2003,[103] the version applicable when these cases were diagnosed.

In order to include all women in each analysis (other than those with missing data that preclude this), we framed our definitions of guideline therapy around the following principle: if the guidelines specify a treatment choice for a woman with a given set of tumor characteristics and other characteristics, and that woman did not receive this treatment (or received a treatment when non-receipt of that treatment was specifically recommended), her treatment within that modality was considered non-concordant. All of the following were considered to be guideline-concordant: (1) if a woman received a treatment that was recommended for her based on her set of tumor characteristics and other characteristics, *or* (2) if she either received or did not receive a treatment that the guidelines characterize as optional (e.g., for some tumor types and sizes the guidelines recommend "considering" adjuvant chemotherapy); or (3) if her tumor characteristics and other characteristics put her in a category for which the 2003 NCCN guidelines did not make recommendations.

Guideline-concordant lymph node sampling: The 2003 NCCN guidelines recommend intra-operative sampling and examination of regional lymph nodes (sentinel lymph node biopsy or dissection) for all women with invasive breast cancer. Therefore, failure to sample at least one lymph node was defined non-concordant. Women for whom information on intra-operative lymph node evaluation was not available (n = 4) were excluded from the analysis.

Guideline-concordant radiation therapy: The 2003 guidelines on post-surgical radiation therapy make recommendations for receipt or nonreceipt (or optional receipt) of radiation according to the type of surgery received and the characteristics of the tumor before surgery, as shown in Figure 3 below.

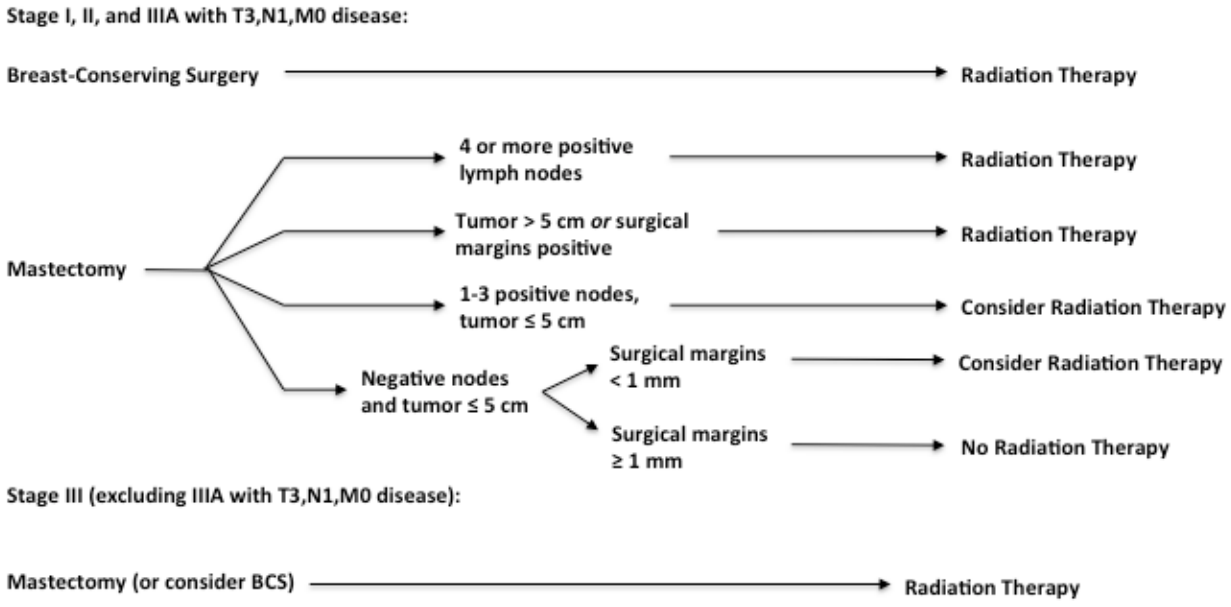


Figure 3. NCCN recommendations for radiation therapy after surgery.

Any patients for whom the guidelines recommended radiation therapy who did not receive this therapy, and any patients for whom the guidelines specified that radiation therapy should not be given who did receive this treatment, were considered to have received non-guideline-concordant treatment (under-treatment and over-treatment, respectively).

Women for whom it was impossible to determine whether treatment was non-guideline-concordant due to missing or incomplete data on tumor characteristics, patient characteristics, surgery, or receipt of radiation were excluded from this analysis (n = 2957). Specifically, this included: (1) women with Stage I, II, or III(T3N1M0) disease for whom surgery type was unknown; (2) women for whom receipt or nonreceipt of radiation therapy was not known, either because there was no record of whether treatment was recommended or given, or because treatment was recommended but it was unknown whether it was administered; and (3) women who were pregnant or lactating at the time of diagnosis (radiation therapy is contraindicated

during pregnancy and it could not be determined from available data whether women pregnant at diagnosis were still pregnant at the time when radiation would have been considered).

Types of radiation included beam radiation, brachytherapy, radioisotopes, a combination of these, and radiation not otherwise specified; all of these were coded, per the POC-BP protocol, as "radiation administered."

Guideline-concordant adjuvant chemotherapy: Based on a patient's tumor characteristics, including tumor size, histology, and other features, the 2003 NCCN guidelines recommended one of the following: give adjuvant chemotherapy; consider adjuvant chemotherapy; or do not give adjuvant chemotherapy (see Figure 4).

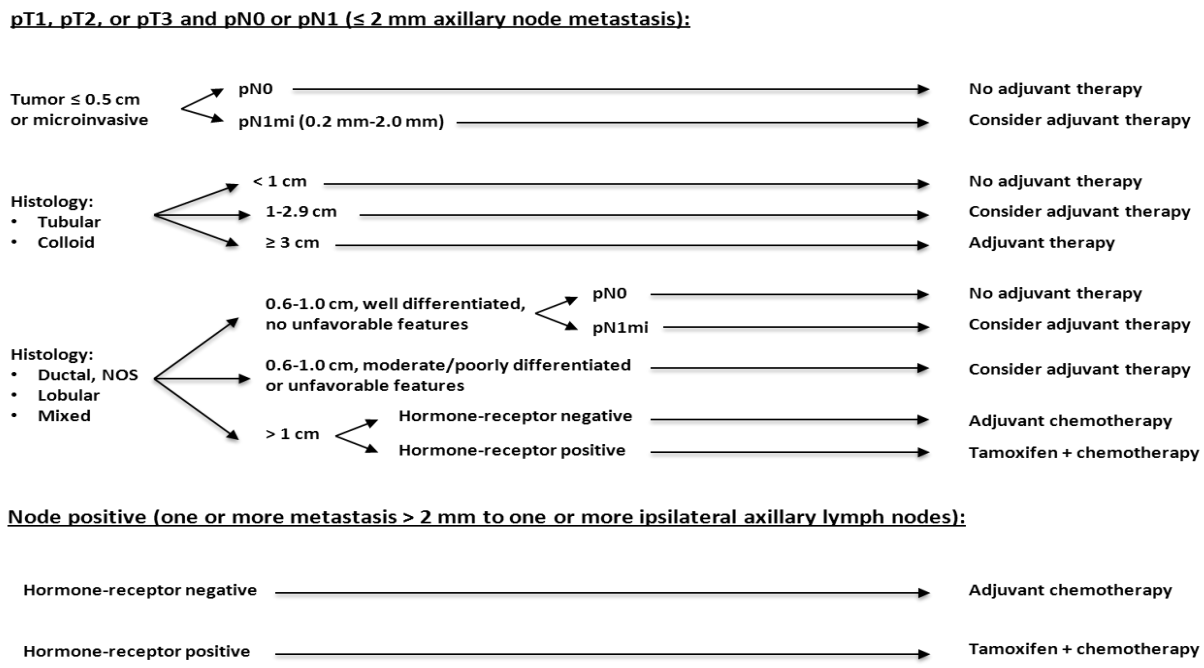


Figure 4. NCCN recommendations for adjuvant chemotherapy based on tumor characteristics in locoregional breast cancer.

Any patients for whom the guidelines recommended adjuvant chemotherapy who did not receive this therapy, and any patients for whom the guidelines specified that adjuvant chemotherapy

should not be given who did receive this treatment, were considered to have received non-guideline-concordant treatment (under-treatment and over-treatment, respectively). The NCCN guidelines in 2003 did not make recommendations regarding chemotherapy for women aged 70 or older or for patients with certain rare histologic tumor types; therefore, women in these categories were automatically classified as having received guideline-concordant treatment, as no treatment choice could be non-concordant. If a patient fit criteria for which the guidelines would make a recommendation and information on whether or not chemotherapy was received was missing, she was excluded from the analysis (n = 191). Patients for whom guidelines would make a recommendation, but for whom missing data on tumor characteristics precluded determining what would be recommended, were excluded as well (n = 8). One patient who did not receive adjuvant chemotherapy because she died before therapy could be initiated was also excluded.

Guideline-concordant adjuvant chemotherapy regimen: Any patients who received non-guideline-concordant adjuvant chemotherapy (under-treatment or over-treatment) was considered to have received a non-guideline-concordant regimen. (In the case of under-treatment, the "non-concordant regimen" was no regimen.) Similarly, in the analysis of guideline concordance in chemotherapy regimen, guideline-concordant nonreceipt of adjuvant chemotherapy was considered a guideline regimen.

Among those patients whose receipt of adjuvant chemotherapy was guideline-concordant, the specific regimen received was considered guideline-concordant only if it was on the list of 2003 NCCN guideline-approved agents, or if it was received as part of a clinical trial protocol. Women in this category whose records did not identify the specific regimen given (other than

trial regimens) were excluded from this analysis. In addition, because the guidelines' list of approved regimens for patients with node-negative disease was more restricted than the list for node-positive disease, any patient with unknown lymph node status who received a regimen approved only for patients with node-positive disease was excluded.

Guideline-concordant hormonal therapy

Hormonal therapy, defined as orally-administered tamoxifen or aromatase inhibitors (AIs), was recommended by the NCCN guidelines for all women with hormone receptor-positive (estrogen receptor (ER)- and/or progesterone receptor (PR)-positive) tumors. Non-receipt of tamoxifen or an AI among women with ER+ and/or PR+ tumors was considered non-concordant (under-treatment), as was receipt of hormonal therapy among women with ER- and PR-negative tumors (over-treatment).

Overall guideline-concordant treatment was defined as guideline concordance in the post-surgical domains addressed in the other Hypotheses (radiation and the three adjuvant systemic therapy components). Women were excluded from the analyses focusing on overall guideline-concordant treatment if missing information on treatments in one or more domains made it impossible to determine whether all therapies received were guideline-concordant.

Dependent Variables: Aim 3

The dependent (outcome) variables for Aim 3 were overall mortality and breast cancer mortality, defined as in the dependent variable descriptions for Aim 1.

Explanatory variables: Aim 1

Body mass index (BMI) category

Body mass index (m/kg^2) was calculated based on information on weight and height, measured at the time of diagnosis, abstracted from physicians' records. In analyses comparing outcomes across BMI categories, cutoffs for the five categories used based on those used by the World Health Organization and the National Heart, Lung, and Blood Institute ("underweight" if BMI<18.5 kg/m^2, "normal" if BMI was 18.5-24.9 kg/m^2, "overweight" if BMI was 25.0-29.9 kg/m^2, "obese" if BMI was 30.0-34.9 kg/m^2, and "very obese" if BMI≥35 kg/m^2).[104]

Explanatory variables: Aim 2

Body mass index (BMI) category, classified as described above.

Explanatory variables: Aim 3

Body mass index (BMI) category, classified as described above.

Guideline concordant therapy

Overall guideline concordant therapy, defined as in the Aim 2 outcome variables description above, was included as a potential mediator in models.

Control variables: Aim 1 and Aim 3

The control variables used in Aim 1 and Aim 3 analyses included age, tumor stage, and other demographic and clinical characteristics (as in the Conceptual Framework). **Age** was defined at the age at time of diagnosis, in years. **Tumor stage** was categorized as defined by American Joint Commission on Cancer (AJCC) staging criteria. T,N,M stages derived from available data were grouped together as Stage I, Stage II, and Stage III.

Demographic Characteristics

Additional demographic variables were included in the regression models if they were known or suspected to be associated with both BMI and mortality, based on the existing literature.

Race and ethnicity information, obtained from patients' medical records and from information found in Indian Health Services patient registration, characterized patients as Hispanic, non-Hispanic White, non-Hispanic Black, non-Hispanic American Indian/Alaska Native (AI/AN), and non-Hispanic Asian Pacific Islander (API).

Insurance status at the time of diagnosis was categorized as private, Medicare or other public insurance only, Medicaid, no insurance, and unknown. The "private" category included patients who had Medicare plus a private supplement. Some other types of public insurance, including TRICARE and military or veterans' insurance, were grouped with Medicare. Women who were dual-eligible for Medicare and Medicaid at the time of diagnosis – a group at high risk for poor outcomes – were grouped in the Medicaid category.

Information on **socioeconomic status and education** was not available on the level of the individual but rather was based on residential census tracts. Patients were categorized based on their place of residence as living in a higher or lower poverty area, with a higher poverty area being one in which ≥ 20% of residents were below the federal poverty level; and as living in a higher or lower education area, where a lower education area was one in which ≥ 25% of adults ≥ 25 years of age had less than a high-school education.

Residential areas, beyond the level of state (or region, in the case of California), are described in the POC-BP data set as 100% urban, mixed, or 100% rural, based on their census tract, using the census-level percent urban/rural variable defined in the 2000 Census.

Clinical Characteristics

Additional clinical variables were included in the regression models if they are known or suspected to be associated with BMI and if they are characteristics that influence mortality risk and/or the NCCN guidelines' recommendations for treatment.

Comorbidity burden is a variable of major importance in the adjusted models related to mortality, both in the consideration of overall mortality and of competing causes of mortality that could affect analyses related to breast cancer mortality. It is also important as a potential confounder in the relationship between BMI category and treatment received, as the guidelines allow, in some circumstances, for consideration of comorbidities in the decision-making process. Comorbidity burden as of the time of diagnosis was characterized using a modification of the Piccirillo (ACE-27) comorbidity index;[105] this considered each of 25 conditions (26 from the Piccirillo comorbidity index, minus obesity and not including the index breast cancer) and assigned a 1-3 score for "level of decompensation," where 1 is Mild, 2 is Moderate, and 3 is Severe. The overall comorbidity score was either based on the single highest-ranking condition or assigned a value of grade 3 if the highest-ranking ailments were grade 2 but they occurred in different organ systems.

Tumor grade was expressed in the POC-BP data set as a I-IV score based on the degree to which cells were differentiated (that is, the degree to which they resembled normal breast tissue), with I being well-differentiated and IV being undifferentiated; grade was also unknown in some cases.

Hormone receptor status was classified as positive where there was positive expression of estrogen receptors (ER) and/or progesterone receptors (PR), negative, or unknown.

Control variables: Aim 2

Demographic Characteristics

Demographic variables were included in the regression models if they were known or suspected to be associated with both BMI and treatment patterns. These demographic variables included age, race, insurance status, census tract-level socioeconomic status, census tract-level educational attainment, and urban or rural residential area, defined as in Aim 1 and Aim 3 models.

Clinical Characteristics

Clinical variables were included in the regression models if they are known or suspected to be associated with BMI and if they are characteristics that may affect treatment choices and/or influence the NCCN guidelines' recommendations for treatment. The clinical variables included in regression models for Aim 2 were the same as those included in the models for Aim 1 and Aim 3, with the exception of tumor AJCC stage. Models for Aim 2 adjusted for tumor size and lymph node status; because of this, AJCC stage was not included to avoid overadjusting.

Tumor size, based on the largest measured dimension of the tumor, was divided into five clinically-relevant categories for the purpose of the adjusted models: ≤ 0.5 cm, 0.51 to 1 cm, 1.01 to 2 cm, 2.01 to 5 cm, > 5 cm, and unknown.

Lymph node status was categorized as positive (one or more positive nodes) or negative, with micrometastases coded as pN1mi counted as negative.

CHAPTER FOUR: PAPER 1 – Obesity and Mortality After Locoregional Breast Cancer Diagnosis

Abstract

Purpose:

Mortality after a diagnosis of invasive breast cancer has been observed to be higher among women who are obese. Given the increasing proportion of women diagnosed with breast cancer who are obese, characterizing and understanding the disparity in outcomes related to women's body size is of significant concern. We investigated the relationship between body mass index (BMI) and all-cause or breast cancer-specific mortality after a diagnosis of locoregional invasive breast cancer.

Patients and Methods:

Women diagnosed in 2004 with Stage I, II, or III breast cancer (n = 5,394) were identified from a population-based, National Program of Cancer Registries-funded Patterns of Care study. Differences in overall and breast cancer-specific mortality were investigated using proportional hazards regression models, in the study as a whole as well as subgroups defined by age and stage.

Results:

An association was observed between BMI and overall mortality (HR for 5 kg/m^2 difference in BMI = 0.93, 95% CI, 0.87 – 0.95; p-value for trend = 0.02), although in analyses stratified according to age category, this association was found to be significant among women aged 70 or older (p-trend = 0.01) but not in women under 70. Body mass index was not found to be associated with death from breast cancer in the sample as a whole, but analyses stratified by AJCC tumor stage showed that among women with Stage I disease, women in the highest

category of BMI had significantly higher mortality (HR for BMI ≥ 35 kg/m^2 versus the reference category, 4.74, 95% CI 1.78 to 12.59; HR for 5 kg/m2 difference in BMI = 1.38, 95% CI 1.22 – 1.55); p-value for trend 0.004).

Conclusion:

Contrary to our hypothesis, higher body mass index was associated with lower overall mortality hazard among women with stage I-III breast cancer; this appeared to be driven specifically by the inverse relationship between BMI and overall mortality found among older women, with a null association among younger women. BMI appeared generally not to be related to breast cancer mortality, but a strong relationship was seen specifically among women with the earliest stage disease. Continued research examining the multifactorial relationships linking obesity and breast cancer outcomes, including characteristics that may modify these relationships, will be important in the ongoing effort to reduce the burden of disease from breast cancer in the future.

Introduction

Although breast cancer treatment advances have substantially reduced mortality among the population of affected women as a whole, particularly among those whose cancer is detected at an earlier stage, research strongly suggests there are persisting disparities in relative mortality between obese and non-obese patients. A substantial amount of evidence suggests not only that postmenopausal obese women are at greater risk for developing breast cancer than postmenopausal women who are not obese,[1] but that breast cancer patients of all ages who are obese are likely to have a poorer prognosis with regard to disease recurrence and mortality.[2-31] Given the large number of women diagnosed with breast cancer each year and the increasing

proportion of those women who are obese, characterizing these disparities and exploring potential mechanisms behind them is important.

Overall Mortality

Existing literature suggests that higher body mass index (BMI) is associated with greater risk of death from any cause following a breast cancer diagnosis.[4-6,10,12,19,32,33] A recent meta-analysis showed that pre-diagnosis BMI was positively associated with all-cause mortality (summary risk ratio = 1.41 for obese women versus those in the "normal" weight category).[10] Some studies do indicate that the association between obesity and overall mortality after breast cancer may differ according to patient characteristics, and may not be present in all subgroups.[4,17,33-36] These include findings by Berclaz et al that the association between BMI and all-cause mortality was significant only among premenopausal women,[4] as well as findings by Kwan et al that higher BMI was associated with overall mortality after breast cancer only among certain racial/ethnic categories.[33] Multiple groups of authors found that obesity was not significantly associated with mortality in women with triple hormone receptor-negative breast cancer,[34-36] although this is a high-risk group in which a ceiling effect may have been present. It should also be noted that many studies linking BMI and mortality after a breast cancer diagnosis describe not a linear trend, but rather a U-shaped curve, with underweight patients also at higher risk of death.[10] However, when taken as a whole, the existing literature strongly indicates that, potentially with the exception of those who are underweight, women with higher BMI at the time of diagnosis are at higher risk of all-cause mortality following a breast cancer diagnosis.

Breast Cancer-Specific Mortality

In addition to the observed relationship between higher BMI and overall mortality, a substantial amount of literature exists suggesting that higher BMI is related specifically to death

from breast cancer.[10,16,17,30,31,33] A recent meta-analysis showed a majority of studies finding a positive relationship between obesity and breast cancer death, with a pooled hazard ratio (HR) for breast cancer mortality of 1.33 compared to non-obese women.[30] Another meta-analysis showed a positive relationship of similar magnitude (HR = 1.26 for obese women compared to non-obese women).[31]

A smaller number of studies indicate, in contrast, that obesity is not associated with breast cancer-specific mortality, or that the association between obesity and breast cancer mortality may be present only among women in certain subgroups defined by menopausal status or other characteristics. For example, Reeves et al found that this association was present only among postmenopausal women,[44] and similarly, Eralp et al found no correlation between BMI and prognosis among women 35 years of age or younger at diagnosis.[45] These findings may be related to differences in the characteristics of breast tumors that tend to occur in younger women and those that occur in older women,[2] and suggest that future studies of breast cancer survival according to BMI should consider a potential interaction with age or menopausal status. More recently, Kwan et al found that, within a California-based study population, higher BMI was associated with greater risk of breast cancer mortality among Latinas and non-Latina white women, but not among African-American and Asian-American women.[33]

However, despite some variations in findings on the presence, universality, and magnitude of the association between BMI and increased breast cancer mortality, no studies have found a significant association between higher BMI and decreased disease-specific mortality, excluding a few subgroup analyses. Studies that show a null, or a very modest, association between obesity and breast cancer prognosis often focused on participants in clinical trials.[4,39,42,47,48]

The observed pattern of higher breast cancer-specific mortality in obese patients likely reflects multiple factors. Obesity is associated with multiple physiological risk factors for breast cancer mortality, including higher levels of endocrine factors related to adipose tissue that are thought to promote tumor progression directly and indirectly.[48,51,52] Chronic inflammation, strongly associated with obesity, influences tumor growth.[48,52] Differential production of adipokines, including leptin and adiponectin, may also be involved in causal pathways linking obesity and breast cancer mortality.[48,52] Obese individuals also tend to have lower levels of serum vitamin D, which has been found to be inversely associated with breast cancer mortality.[54] In addition to these biological mechanisms, obese patients have larger tumors at treatment onset due in part to delayed diagnosis, which can result from differences in screening patterns.[48,55-57] Systematic differences in the postsurgical treatment received by patients with higher and lower BMI may also exist, some of which may be related to sociodemographic and clinical factors closely correlated with BMI. It is therefore important to examine the relationship between BMI and breast cancer mortality over an extended period of time, in a diverse population, accounting for potentially influential sociodemographic factors, clinical characteristics, and comorbidities, in order to attempt to isolate the independent effect of adiposity on breast cancer mortality. In this way, we conducted our analysis as a necessary first step in discerning the mechanisms behind the relationship between obesity and breast cancer outcomes. We compared overall mortality and breast cancer-specific mortality between women according to BMI using data on individuals with breast cancer identified from population-based cancer registries in seven states, hypothesizing that breast cancer-specific mortality would be higher among women with greater BMI and that overall mortality would be higher among both underweight and obese women.

Data and Methods

Data Sources

This study used data from the National Program of Cancer Registries (NPCR) Breast and Prostate Cancer Data Quality and Patterns of Care Study (POC-BP) to examine the relationships between patient body mass index (BMI) and mortality after a breast cancer diagnosis. The POC-BP data set comprised breast and prostate cancer cases diagnosed in 2004 identified from population-based cancer registries in California, Georgia, Kentucky, Louisiana, Minnesota, North Carolina, and Wisconsin. Cases were selected for inclusion using stratified random sampling based primarily on racial and ethnic characteristics, but also including state-specific regional factors. Registry information was supplemented with information abstracted from medical records from hospitals and physicians' offices. Follow-up data on women's vital status were collected through the routine linkage of cancer registry data with death certificate data from state vital statistics departments as well as through NPCR-supported use of the National Death Index (NDI), which enabled identification of deaths occurring in states other than the one in which a patient was diagnosed.[101]

Eligibility Criteria

Women 20 years or older diagnosed with primary breast cancer in 2004 (other than by autopsy or death certificate) were eligible for POC-BP if they had no previous diagnoses of *in situ* or invasive breast cancer, other reportable cancers, Paget's disease, Kaposi's sarcoma, or lymphoma. Cases were selected from registries using random sampling stratified by race/ethnicity, as well as Appalachian/non-Appalachian region in North Carolina and Kentucky, facility type and volume in Wisconsin, and urban-rural status in Georgia.

The focus of this analysis was locoregional invasive disease. A total of 6,967 patients with Stage I, II, or III disease were identified. Women who did not receive any surgery for their breast cancer (n = 105) were excluded from analyses due to the possibility that some women may not have had surgery because of metastatic disease discovered after the initial characterization of their tumors for registry purposes. Women with unknown BMI (n = 1462) were also excluded. Finally, women for whom no vital status follow-up data were available (n = 6) were excluded, leaving 5,394 cases.

Explanatory Variables

Body mass index (m/kg^2) was calculated based on weight and height information abstracted from physicians' records. Weight and height were measured at the time of diagnosis.

Outcomes

Time to death (all-cause, or overall, mortality) was defined as days between diagnosis and death from any cause. Time to death from breast cancer was defined as days between diagnosis and breast cancer-specific death, as determined from ICD-10 codes for cause of death recorded in cancer registry databases. Survival analyses included data on women's vital status through 8 years after the date of diagnosis (2004-2012).

Clinical and Demographic Covariates

Patient age was determined at time of diagnosis. Race/ethnicity information was obtained from patients' medical records, and from information found in Indian Health Services patient registration. When Hispanic origin was unclear, an identification algorithm developed by the North American Association of Central Cancer Registries was used.

Insurance status was categorized as private, Medicare or other public insurance only, Medicaid, uninsured, and unknown. The "private" category included patients with Medicare plus

private supplemental insurance. Women who were dual-eligible for Medicare and Medicaid were grouped in the Medicaid category.

Education and socioeconomic status were based on census tract information for the patient's place of residence. Patients were categorized as living in a higher poverty (≥ 20% of residents below the federal poverty level) or lower poverty area, and as living in a lower education (≥ 25% of adults ≥ 25 years of age with less than high-school education) or higher education area. Residential areas were described as 100% urban, mixed, or 100% rural, using the 2000 U.S. Census Bureau's urban and rural criteria.

Tumor pathologic stage was categorized as I, II, or III, as defined by American Joint Commission on Cancer (AJCC) staging criteria. Tumor grade was characterized by a I-IV score based on the degree to which cells were differentiated (that is, the degree to which they resembled normal breast tissue), with I being well-differentiated and IV being undifferentiated; grade was also unknown in some cases. Hormone receptor status for each of the hormone receptor types included in analyses – estrogen receptors (ER) and progesterone receptors (PR) -- was classified as positive, negative, or unknown.

To provide a characterization of the comorbidity burden present at the time of diagnosis, a modification of the Piccirillo (ACE-27) comorbidity index[105] was used; this considered each of 25 conditions (26 from the Piccirillo comorbidity index, minus obesity and not including the index breast cancer) and assigned a 1-3 score for "level of decompensation," where 1 is Mild, 2 is Moderate, and 3 is Severe. The overall comorbidity score was either based on the single highest-ranking condition or assigned a value of grade 3 if the highest-ranking ailments were grade 2 but they occurred in different organ systems.

Statistical Analysis

Overall mortality and breast cancer specific mortality were compared across BMI categories, based on cutoffs defined by the World Health Organization ("underweight" if BMI<18.5 kg/m^2, "normal" if BMI was 18.5-24.9 kg/m^2, "overweight" if BMI was 25.0-29.9 kg/m^2, "obese" if BMI was 30.0-34.9 kg/m^2, and "very obese" if BMI≥35 kg/m^2). Hazard ratios (HR) and 95% confidence intervals for each outcome were estimated using Cox proportional hazards models with survey weights and stratification to account for the POC-BP sampling. Covariates were chosen *a priori* because of a known or potential relationship with BMI and with treatment choices, and included race/ethnicity, health insurance, education, socioeconomic status, tumor registry, urban/rural residence, tumor size, tumor grade, hormone receptor status, and comorbidities. The models incorporated stratification and sampling weights to account for the POC-BP sampling design. We calculated p-values for trend for each model by running a second version of the model in which BMI was represented by a continuous variable.

Results

Table 1 shows BMI according to demographic and clinical characteristics of the study population. The mean BMI was 29.1 kg/m^2 and the median, 28.0 kg/m^2. Age at diagnosis ranged from 20 to 98 years. Most women (86%) were 40 to 79 years of age at the time of diagnosis. Age and BMI at time of diagnosis were associated ($p < 0.001$); mean BMI was greater in higher age categories, except for among women ages 70-79 and women 80 years of age and older, the latter category of which had the lowest BMI. Age-adjusted, survey-weighted analyses were conducted to examine associations between BMI and other demographic and clinical variables.

Most women (75.6%) were white. Race/ethnicity was associated with BMI ($p < 0.001$), with black women having the highest mean BMI (31.0) and Asian/Pacific Islander women having the

lowest mean BMI (24.4). The majority of women had private insurance (62.9%) or had Medicare or other public insurance as their only insurance type (21.2%). Insurance status was also associated with BMI ($p < 0.001$); women with private insurance had the lowest mean BMI (27.9) while women who had Medicaid insurance had the highest mean BMI (29.8). The majority of women (69%) lived in a census tract where more than 75% of adults had a high school level of education or higher. Residence in a lower education area or a higher poverty area was associated with higher BMI ($p < 0.001$ for both). The mean BMI among women in a lower education area was 29.8, compared to 27.8 in higher-education areas, and the mean BMI among women in a higher poverty area was 29.1, compared to 28.1 in lower poverty areas. About half of women lived in an urban area, a third in an area characterized as mixed urban and rural, and the remainder in a rural area. Urbanicity was associated with BMI ($p < 0.001$); women in urban areas had the lowest mean BMI (28.0) while women in rural areas had the highest (28.9). State of residence at the time of breast cancer diagnosis was also associated with BMI ($p < 0.001$).

Most women had stage I (48.4%) or stage II (37.6%) breast cancer. AJCC stage was associated with BMI ($p < 0.001$), with women diagnosed with stage III tumors having the highest mean BMI (29.4) and women with stage I disease having the lowest (27.6). The majority of women (61.6%) had lymph node-negative disease. Lymph node status was associated with BMI ($p < 0.001$); women with node-positive disease (one or more positive nodes) had a higher mean BMI (28.9) than women who had node-negative disease (28.0). Women whose lymph node status was not recorded had a substantially lower mean BMI of 27.2. The majority of tumors (83.7%) were 0.5 to 5 cm in size. Tumor size was also associated with BMI ($p < 0.001$). It is notable that women whose tumor size was not found in a registry or other records (n = 59) had the highest mean BMI (31.1). Among women whose tumor size was recorded, greater tumor size

was associated with higher BMI, with women whose tumors were 1 cm or smaller in greatest dimension having a mean BMI of less than 28 and women whose tumors were over 5 centimeters having a mean BMI of 29.5. Most women (73.2) had ductal carcinomas. Tumor histology was associated with BMI ($p = 0.02$); women with mixed ductal and lobular carcinomas had a significantly lower mean BMI of 27.1 compared to 28.3-28.4 among women with ductal, lobular, or other histologic types. Most women had tumors that were grade II (moderately differentiated, 39.0%) or grade III (poorly differentiated, 35.8%). There was a borderline statistically significant positive association between grade and BMI ($p = 0.07$). Most women (73.0%) had tumors that were estrogen receptor-positive (ER+) and/or progesterone receptor-positive (PR+). Having an ER+ and/or PR+ tumor was not associated with BMI ($p = 0.13$). In separate analyses (results not shown) ER+ status, considered without regard to PR+ status, also showed no association with BMI ($p = 0.17$), while a borderline statistically significant relationship between progesterone receptor-positive (PR+) status and BMI was found ($p = 0.05$); women with PR+ tumors had higher mean BMI (28.5) than those with PR- tumors (27.9). About half of women (49.7%) had tumors that were human epidermal growth factor 2 (HER2)-negative. HER2 receptor status was not associated with BMI ($p = 0.93$).

Comorbidity scores were low for most women; 45% had a comorbidity score of 0 and 44% had a score of 1. Comorbidity burden was associated with BMI ($p < 0.001$), although not in a linear fashion. While the lowest mean BMI (26.4) was found among women with a comorbidity score of 0, the highest mean BMI was found among women with a score of 1.

Five-year all-cause mortality was 14% and five-year breast cancer-specific mortality was 9.5%. As would be expected, both all-cause and breast cancer-specific mortality differed according to AJCC stage at diagnosis (Table 2). At eight years after the date of diagnosis, 19.2%

of women were known to be deceased (1033 deaths), with half of these deaths from breast cancer (514 breast cancer deaths, 49.8%), and the remainder (all but 5 women) had been censored because vital status data were no longer being collected (Table 2).

Figures 1 and 2 present Kaplan-Meier curves describing all-cause mortality and breast cancer-specific mortality, respectively, according to BMI category. Table 3 shows results of proportional hazards regression models investigating the relationship between BMI and all-cause or breast cancer-specific mortality.

All-cause mortality

After adjusting for clinical and demographic characteristics, women with a BMI of 30-34.9 kg/m^2 appeared to have a lower hazard for all-cause mortality (HR for a 5 kg/m^2 difference in BMI = 0.93, 95% CI, 0.87 – 0.95; p-value for trend = 0.02). This association between BMI and all-cause mortality was found to vary according to age at diagnosis (Table 4; p-value for interaction = 0.01). Among women under 50 years of age or between 50 and 69 years of age, there was no significant association between BMI and overall mortality, but among women age 70 and older, BMI was inversely related to overall mortality (p-value for trend = 0.01). In particular, women with BMI < 18.5 kg/m^2 had a significantly elevated mortality hazard compared to women with a BMI of 18.5-24.9 kg/m^2 (HR = 1.72, 95% CI 1.03 to 2.89) and there was a suggestion that women in higher BMI categories had a lower mortality hazard (HR for BMI of 25-29.9 kg/m^2, 30-34.9 kg/m^2, and 35 kg/m^2 or greater compared to women with a BMI of 18.5-24.9 kg/m^2 = 0.84, 0.73, and 0.78, respectively; 95% CIs for these estimates were 0.63-1.14, 0.51-1.05, and 0.52-1.17, respectively). In an analysis (not shown) in which women over 70 were examined with underweight women (BMI < 18.5 kg/m^2) excluded, the association between higher BMI and lower overall mortality hazard remained significant as gauged by the p-

value for linear trend (p = 0.02), with hazards ratios for the 25-29.9 kg/m^2, 30-34.9 kg/m^2, and ≥ 35 kg/m^2 categories very similar to those found in all women over 70 (0.84, 0.77, and 0.84, respectively).

In models stratified according to AJCC stage (Table 5), no significant differences were observed in the HR estimates for each stage, and indeed within each stage-specific model the BMI-overall mortality relationship was not significant. The stage-stratified analysis was conducted for descriptive purposes, as a test for interaction between BMI and AJCC stage with regard to all-cause mortality was not significant (p = 0.83 for interaction term).

We explored whether the association between BMI and all-cause mortality might vary according to race/ethnicity or tumor registry. No significant interactions were observed (p = 0.08-0.73 for interaction terms with registries, and 0.53-0.95 for interactions with racial/ethnic categories).

Breast Cancer Mortality

BMI was not found to be associated with breast cancer-specific mortality in models using stage I, II, and III cancer patients and adjusting for age, AJCC stage, and other demographic and clinical characteristics (p-value for trend = 0.42; Table 3). However, in models stratified according to AJCC stage (Table 6), specifically among patients with Stage I tumors, women with BMI ≥ 35 kg/m^2 were found to have over four times the breast cancer mortality hazard (HR = 4.74, 95% CI 1.78 to 12.59) of women with a BMI of 18.5-24.9 kg/m^2 (p-value for trend = 0.004; HR for 5 kg/m^2 difference in BMI = 1.38, 95% CI 1.22 – 1.55), while among women with Stage II and Stage III tumors, no relationship between BMI and breast cancer mortality was observed.

The association between BMI and breast cancer mortality was not found to differ according to age, or race/ethnicity, or tumor registry ($p = 0.31$, $p = 0.53$-0.96, and $p = 0.14$-0.94, respectively).

Discussion

In this study, we examined overall mortality and breast cancer mortality according to BMI among women with locoregional disease followed for five to eight years after diagnosis. At five years, a common assessment point for survival after breast cancer and a time at which complete data were available from all registries represented in the study, 14% of women had died of any cause, with roughly two-thirds (68%) of these deaths due to breast cancer as the primary cause.

Contrary to our hypotheses, higher body mass index was not associated with higher breast cancer mortality in the full sample of women included in analyses, and higher BMI was actually associated with lower overall mortality hazard among women with stage I-III breast cancer, albeit only among older women over 70 years of age. Among women in this age category, mortality hazard was substantially higher among underweight women, but the association between BMI and mortality remained in an analysis in which women with a BMI less than 18.5 kg/m^2 were excluded, suggesting that having a higher BMI (rather than simply not being underweight) may confer benefit among older women. The association between BMI and overall mortality did not differ according to AJCC stage or according to race.

The significant relationship between higher BMI and lower mortality among older women may be partially explained by a correlation between higher BMI and better functional status and overall health among older adults. It is furthermore possible that our method of adjusting for comorbidities did not completely capture comorbidity burden; older women with lower BMI,

particularly women who were underweight, may have been more likely to have undiagnosed comorbid conditions or diseases not accounted for in the framework of the Piccirillo index. The finding that, at least for some women, being underweight was significantly associated with higher mortality was thus not contrary to our hypothesis. It should be noted, however, that our findings from analyses focusing on women age 70 or over who were not underweight suggest that poorer outcomes in older women related to being underweight do not entirely explain the observed association – that is, that having higher BMI, rather than simply not being underweight, may have a protective effect. This finding is in line with some previous research documenting an inverse relationship between BMI and mortality among older individuals in the general population, in a pattern referred to as an "obesity paradox" or "reverse epidemiology."[106]

It is nevertheless surprising, given previous findings, that there was a null relationship between BMI and all-cause mortality among women under age 70. It is true that some other researchers have found a difference in the relationship between BMI and mortality according to age; however, even among these studies, a null BMI-mortality relationship among younger women and inverse relationship among older women has generally not been observed. More commonly, researchers have found that higher BMI is associated with poorer outcomes only among younger women, with no significant relationship found among older women. Berclaz et al, in a secondary analysis of International Breast Cancer Study Group data, determined that women with higher BMI had significantly worse outcomes only within the pre- or peri-menopausal group, but did not observe the inverse relationship between BMI and mortality in older women that we saw.[4] Similarly, Vitolins and colleagues did not observe an inverse association between BMI and mortality in older adults, but did find that the relationship between BMI and cancer death was strongest in younger age categories and was not significant in the

highest age category examined.[28] It should be noted that these authors' data included women with a maximum age at diagnosis of 73, and that therefore it cannot be determined whether their findings would have been similar to ours had they included a greater number of older women. Both Berclaz et al and Vitolins et al used data on women who had been enrolled in clinical trials. These women probably had fewer and less severe comorbidities due to trial exclusion criteria, and may not have represented the general population, particularly older women among whom comorbidities and complex medical conditions are more common. Abrahamson et al found that women aged 20-54 at time of diagnosis had significantly higher all-cause mortality if they were obese, in a study notable for using multiple objective measures of body size (measured height, weight, and waist-to-hip ratio).[2] Daling and colleagues also found BMI was a strong predictor of mortality in women aged 45 or younger at time of diagnosis; this was a somewhat older study, but large and population-based.[11]

Not all studies that included women with a range of ages have found a difference according to age in the relationship between BMI and mortality.[10,26,30,31,41] The meta-analyses by Niraula et al and Protani et al both indicated hazard ratios for all-cause mortality were slightly higher among premenopausal women compared to postmenopausal women, but not significantly so.[30,31] Nichols et al observed elevated hazard for all-cause mortality among women whose pre-diagnosis BMI was in the higher categories as well as women with BMI in the underweight category, but did not find that this association was modified according to age or menopausal status.[26] While Nichols and colleagues used a data set including BMI calculated from self-reported weight and height one to five years before diagnosis, the tumor stages and other characteristics in their study were similar to ours, making the contrasting finding notable.

Our findings regarding breast cancer-specific mortality were, as mentioned earlier, also surprising. Contrary to our hypothesis, in the full group of women included in our analysis, higher BMI was not associated with higher mortality from breast cancer. However, among women with Stage I cancer specifically, an association along the lines we expected was found, with women in the highest BMI category having a substantially greater hazard for breast cancer mortality. The BMI-mortality relationship was significant only among women in this category (those with BMI of 35 kg/m^2 or greater). In women with Stage II or Stage III cancer, a null relationship between BMI and breast cancer mortality was observed. Investigations of possible effect modification by tumor registry or by race did not show any difference in the BMI-breast cancer mortality relationship according to these factors. We also, notably, did not observe a difference in the BMI-breast cancer mortality relationship according to age, in contrast to our findings regarding overall mortality (potential interactions according to whether women had gone through menopause could not be investigated because data on menopausal status were not available). In this regard we did not replicate findings that had provided, in part, the motivation to examine this potential interaction.[44,45] However, the existing literature is far from reflecting a consensus on whether age, or menopausal status, modifies any relationship between obesity and breast cancer mortality.[6]

The finding that BMI was associated with breast cancer mortality only among women with lower stage disease contrasts with some previous findings,[6,10,12,14,16,26] but it is in line with a number of previous reports. Kroenke et al, reporting on data from the Nurses' Health Study, also found that BMI was significantly associated with death due to breast cancer only among women with less advanced disease, which they defined according to tumor size and lymph node involvement separately.[18] Newman et al observed in another cancer registry-based study that

BMI was associated with an elevated risk of death from breast cancer only among women with no positive lymph nodes (who would generally have a lower stage).[107] Tretli and colleagues also had very similar findings; in a Norwegian Cancer Registry-based study, they determined that BMI was a prognostic factor with regard to breast cancer mortality among women with Stage I or II disease but not among women whose breast cancer was stage III or IV, and that among the women with early stage disease, the association was significant and substantial for the most part only among women in the highest quintile of BMI.[50] Some of the earliest studies focusing on BMI and breast cancer mortality also reported a similar pattern,[108,109] prompting the authors to suggest that effects of BMI are more apparent among women with generally better prognostic features. This is perhaps the most likely explanation for these findings, but further research could be directed at determining whether other factors may contribute. For example, it has been observed that women with higher BMI are more likely not only to have a delayed diagnosis, but also more likely to erroneously have their disease characterized as less advanced than it actually is, due to technical challenges to the typical staging procedures.[50] These challenges would be greater in women in the very obese category, suggesting they would have an even greater likelihood of having their tumors erroneously given a stage I characterization. Continued attention to the possibility of statistical artifacts related to this issue should be a part of future study designs. As technologies make accurate staging easier, and as research continues to identify prognostic features beyond the typical T,N,M stage, it will also be important to consider whether there continues to be an apparent association between BMI and disease-specific mortality among women with an earlier assigned tumor stage, or in otherwise defined favorable prognostic categories.

Strengths and Limitations

In our analyses of overall and breast cancer mortality, we made use of a large sample of patients all diagnosed in the same year with locoregional disease, but representing diverse geographic areas, racial/ethnic categories, and socioeconomic characteristics. The POC-BP data set was more complete than some registry-based studies due to the additional resources made available to the investigators to verify data and collect more detailed information on factors including comorbid conditions. The study benefited from a relatively long follow-up period, with up to eight years' worth of data from most of the tumor registries represented, although given improved rates of breast cancer survival, even longer follow-up in such studies should be a priority.

This study's findings should be considered in light of some important limitations. While the sample size was large, at over 5,000 women, the analyses may still have suffered from a lack of power, particularly those involving subsamples, because due to generally good prognosis, particularly among women with early stage disease, the number of events (deaths, and in particular breast cancer deaths) was relatively small. Similarly, while the follow-up time was longer than in many studies, at five to eight years, additional follow-up data could have been helpful, especially with examining breast cancer mortality. In contrast to our study, two large studies conducted in Denmark, each with up to 30 years of follow-up, observed significant long-term differences in breast cancer mortality according to BMI.[14,16] The fact that women in these studies were diagnosed as early as 1976, with substantial changes in diagnosis and treatment both in Denmark and the U.S. occurring since then, makes the study populations less comparable to our own and those in other more modern studies; however, the obvious benefit is the authors' ability to describe longer-term differences in outcomes according to BMI. A longer follow-up period could substantially strengthen future iterations of the present study. Another limitation

related to follow-up was that not all tumor registries collected and provided data for the same length of time. Follow-up data for the full 8 years for all women would have improved statistical power, but we do not consider it likely that the difference in extent of follow-up data collection by registry biases our results, because our statistical models account for tumor registry.

A particular challenge related to sample size was the fact that there were only 78 women in the "underweight" category, making it difficult to examine outcomes in this group. It should be noted, however, that our findings do suggest this is a group who may differ in important regards from women in the "normal"-weight category, and that future analyses should continue, if possible, to consider and investigate this difference.

There were also, despite the oversampling included in the POC-BP study design, low numbers of women in some racial/ethnic subgroups. In particular, women of Native American/Alaska Native heritage were not well represented, raising concerns about the generalizability of our findings to women in this high-risk group.

Another notable limitation, albeit one that is ubiquitous in the literature on this topic, is the use of body mass index as a proxy for adiposity. BMI is not a precise or consistent means of characterizing body composition,[110,111] is problematic at the extremes of height, and may exhibit systematically larger inaccuracies among women with increasing age[110]; however, it is frequently used, as in this retrospective analysis, in the absence of other available or feasible measures. Therefore, while our study suffers from a limitation in this regard, it is also methodologically consistent with much of the literature.

Missing data on height and/or weight pose a potential threat to the validity of our findings. 21.3% of the women in the parent data set who were eligible to be included in the analytic data set were excluded due to missing data on weight, height, or both. These data are likely,

furthermore, not to be missing completely at random, if for no other reason than the fact that women receiving chemotherapy are more likely to have weight documented in their medical charts. We assessed potential relationships between missing weight and/or height and important clinical and demographic variables using age-adjusted linear regression models, and then conducted a sensitivity analysis in which missing weight or height was imputed among women whose records showed one but not the other. Results from these analyses are presented in a supplement to this paper (see Appendix B and Table C3 in Appendix C). Briefly, we found that several demographic and clinical variables were associated with likelihood of missing weight and/or height data, but that those characteristics associated with missing BMI were not consistently favorable or unfavorable for prognosis (for example, older women were more likely to have missing BMI, but a greater probability of missing BMI was also found among women with lower AJCC stage), making it difficult to determine in what direction, if at all, results may reflect a bias due to the unavailable data. Models using BMI based on imputed height or weight where data were unavailable resulted in findings very similar to those from our main analyses reported here. Another missing data issue, less central to the main analyses performed but still a notable limitation, was the fact that women's menopausal status was unknown. Thus, while we were able to conduct analyses stratified according to age, we were unable to examine potential interactions according to menopausal status.

Finally, while they did not for the most part emerge as important independent predictors of the outcomes examined, it should be noted that education and socioeconomic status (poverty) were measured at the census-tract level, rather than the level of the individual, which would have provided more precision with regard to SES as a potential contributor to mortality.

Implications

Although our investigation did not replicate the findings of some previous studies linking greater BMI to higher breast cancer mortality in the general female breast cancer population, we did identify women with Stage I disease as a group in which obesity, particularly greater than moderate obesity, was strongly linked to poorer outcomes with regard to breast cancer death. With continued improvement in diagnostic techniques and screening practices, we can expect to see more women diagnosed with early stage disease, making it even more important to try to understand and address disparities in outcomes within this population. Another notable finding was the inverse relationship between BMI and all-cause mortality among older women above age 70 at the time of diagnosis. The average life span of women is now well above 70 and continuing to increase, and many women are diagnosed at a later age. It is therefore of critical importance to determine whether, perhaps due to differences in tumor characteristics, comorbidities, or other factors, body weight and adiposity may have differing effects on outcomes in this subgroup.

Conclusion

This study examined overall mortality and breast cancer mortality among women with locoregional invasive breast cancer. It adds to the existing evidence by drawing on a population-based sample of women diagnosed in the same year with Stage I, II, or III disease in seven different geographic regions and followed for five to eight years. Continued research examining the multifactorial relationships linking obesity and breast cancer outcomes, including factors that may modify these relationships, will be important in the ongoing effort to reduce the burden of disease from breast cancer in the future.

Figures and Tables

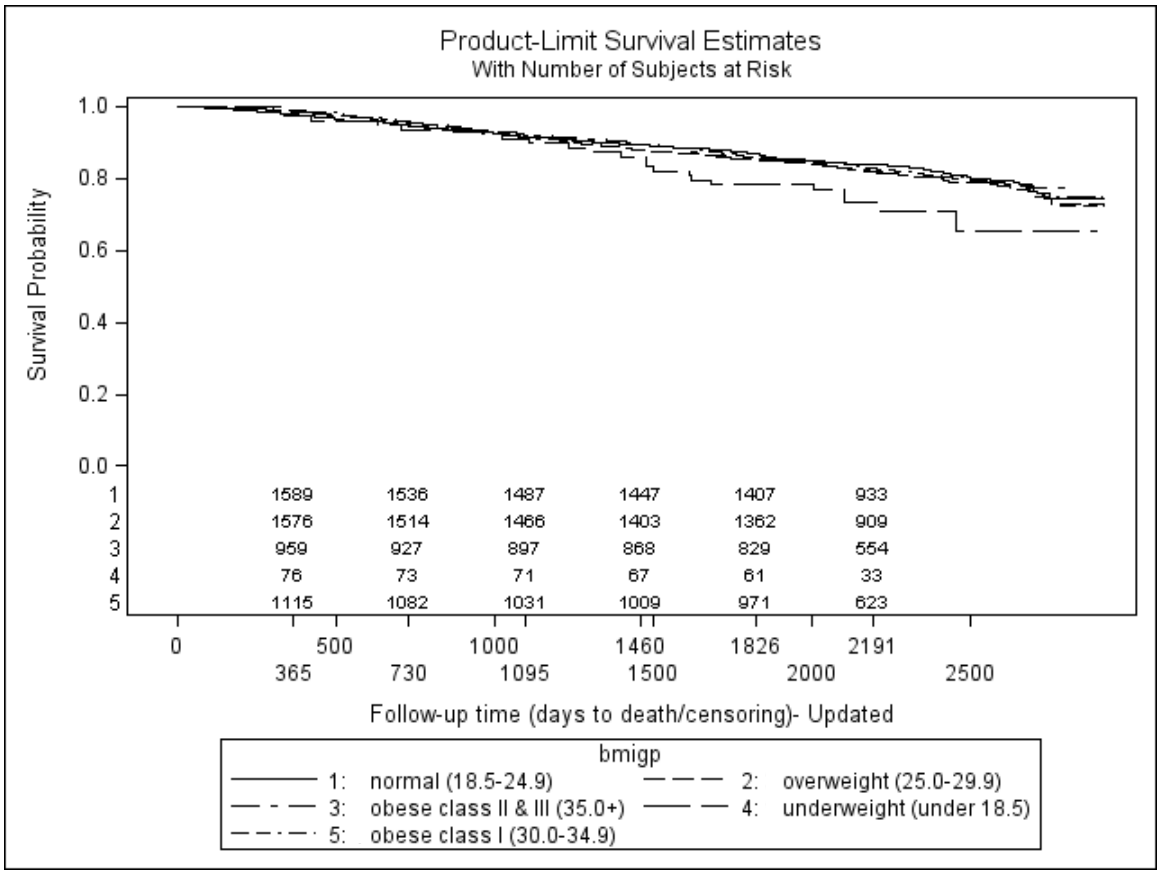
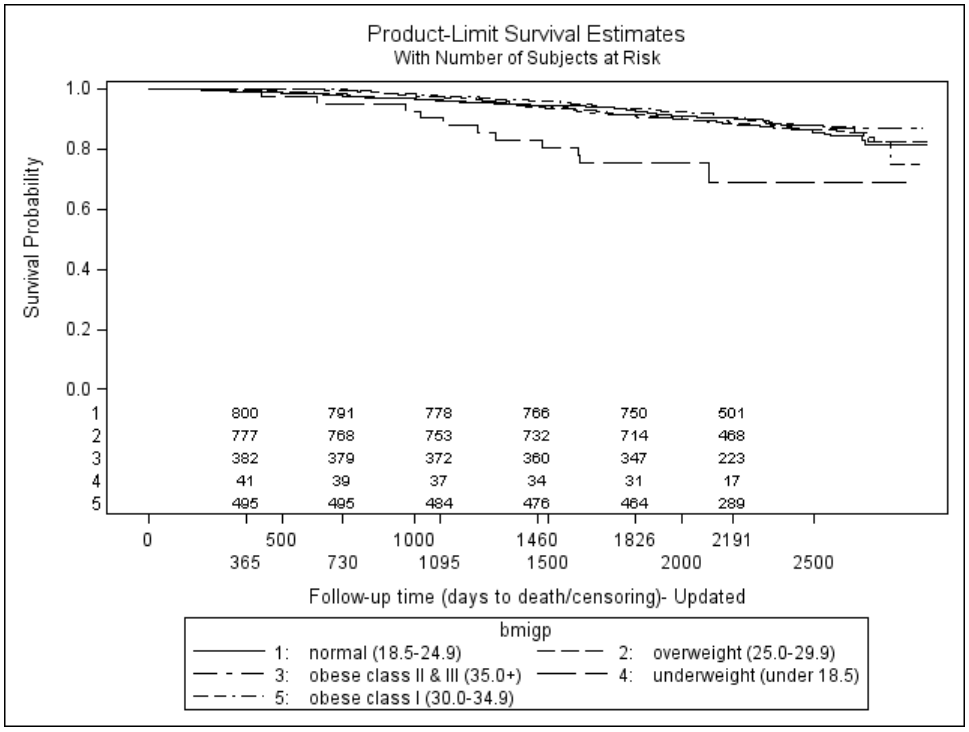


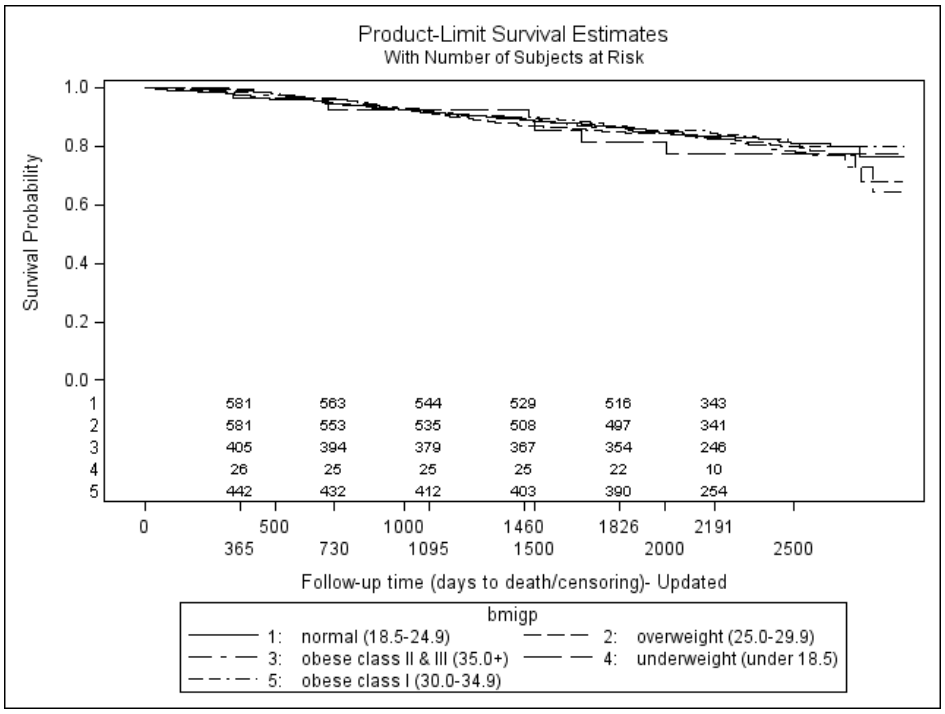
Figure 1a. Kaplan-Meier curves describing overall mortality according to BMI category.
p-value for test of equality over strata = 0.20.

(Below) Figure 1b, parts A-C. Kaplan-Meier curves describing overall mortality according to BMI category, stratified by AJCC stage (top to bottom, stages I, II, and III). P-values for tests of equality over strata: (A) stage I, p = 0.23; (B) stage II, p = 0.96; (C) stage III, p = 0.19.

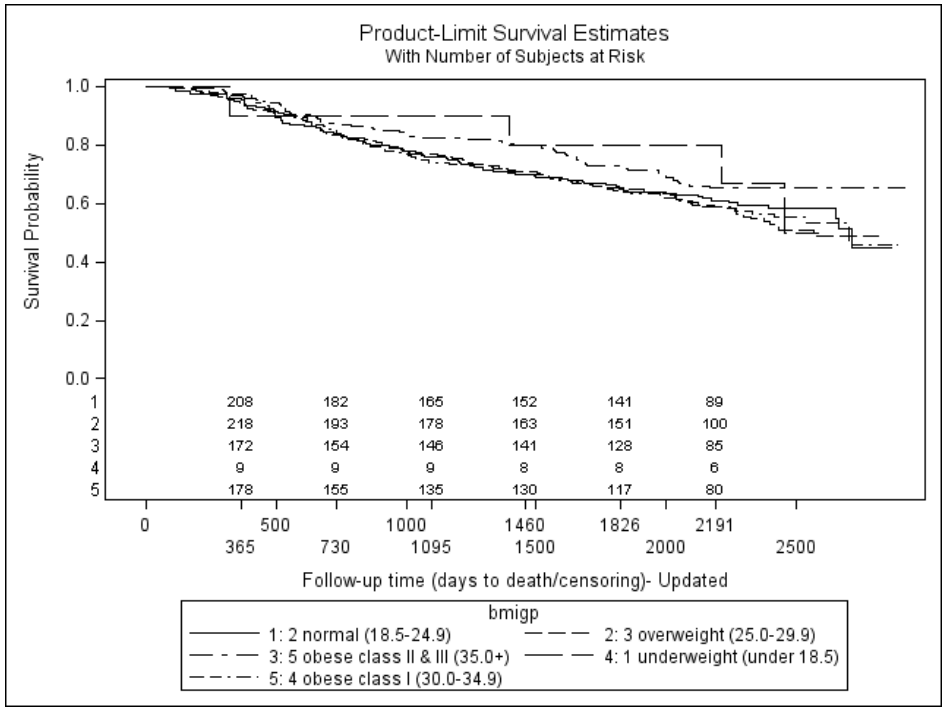
A.



B.


Product-Limit Survival Estimates
With Number of Subjects at Risk
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
1 581 563 544 529 516 343
2 581 553 535 508 497 341
3 405 394 379 367 354 246
4 26 25 25 25 22 10
5 442 432 412 403 390 254
0 500 1000 1460 1826 2191
365 730 1095 1500 2000 2500
Follow-up time (days to death/censoring)- Updated
bmigp
1: normal (18.5-24.9)
2: overweight (25.0-29.9)
3: obese class II & III (35.0+)
4: underweight (under 18.5)
5: obese class I (30.0-34.9)

C.


Product-Limit Survival Estimates
With Number of Subjects at Risk
Survival Probability
1.0
0.8
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0.2
0.0
1 208 182 165 152 141 89
2 218 193 178 163 151 100
3 172 154 146 141 128 85
4 9 9 9 8 8 6
5 178 155 135 130 117 80
0 500 1000 1460 1826 2191
365 730 1095 1500 2000 2500
Follow-up time (days to death/censoring)- Updated
bmigp
1: 2 normal (18.5-24.9)
2: 3 overweight (25.0-29.9)
3: 5 obese class II & III (35.0+)
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5: 4 obese class I (30.0-34.9)

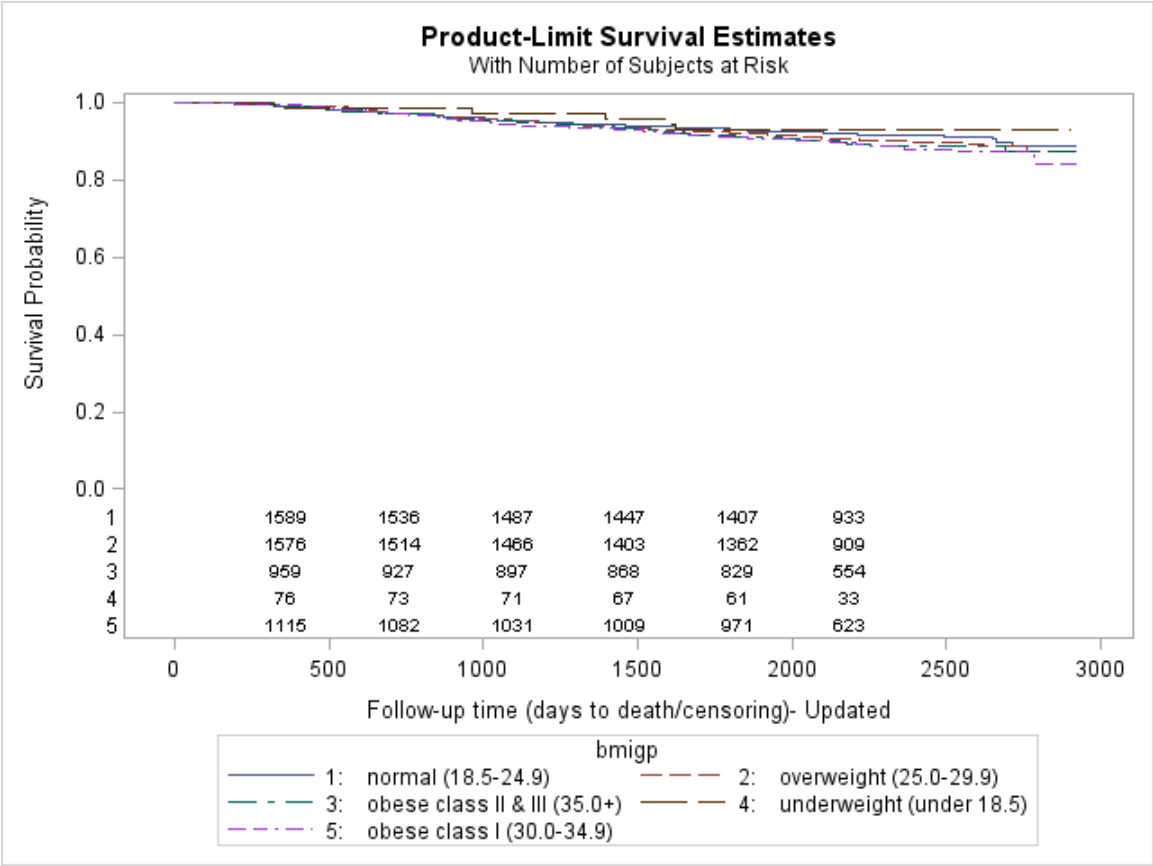
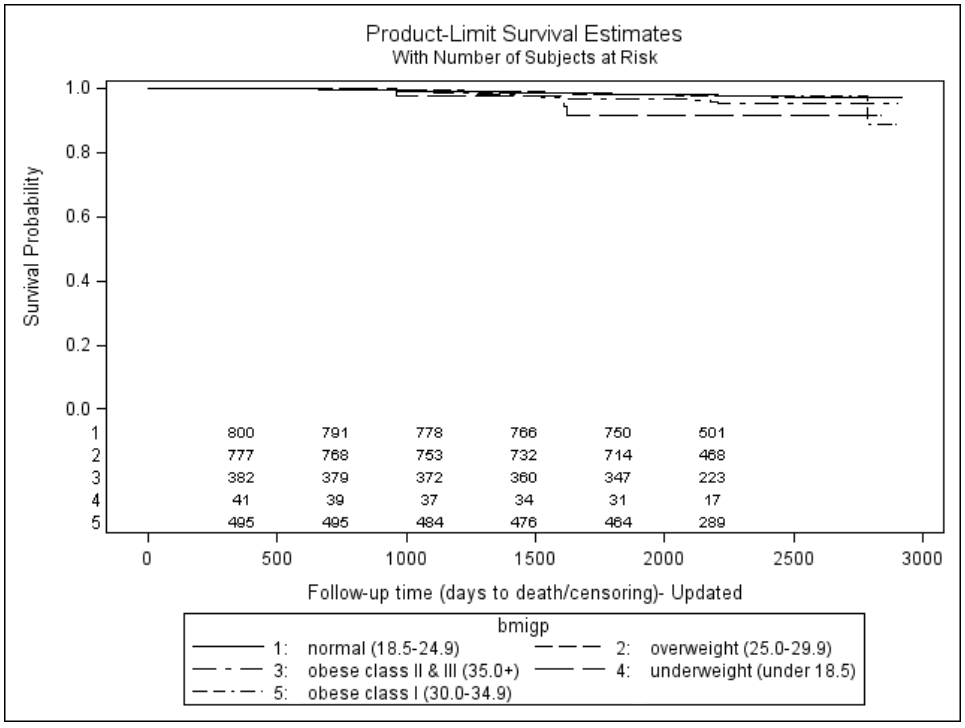


Figure 2a. Kaplan-Meier curves describing breast cancer-specific mortality according to BMI category. p-value for test of equality over strata = 0.12.

(Below) Figure 2b, parts A-C. Kaplan-Meier curves describing breast cancer mortality according to BMI category, stratified by AJCC stage (top to bottom, stages I, II, and III). P-values for tests of equality over strata: (A) stage I, p = 0.09; (B) stage II, p = 0.55; (C) stage III, p = 0.37.

A.



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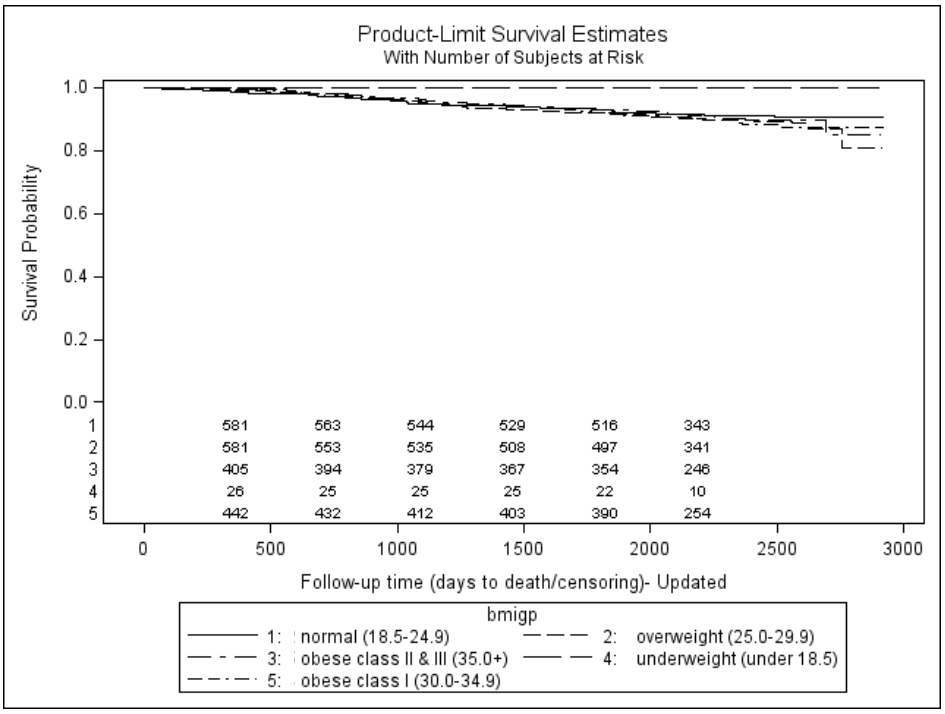
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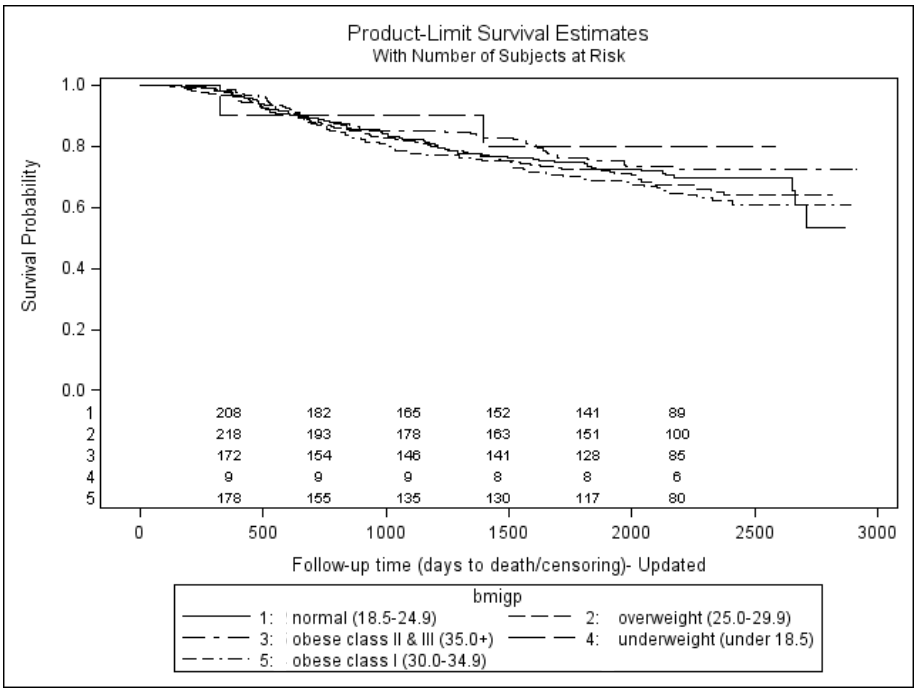
C.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2 218 193 178 163 151 100
3 172 154 146 141 128 85
4 9 9 9 8 8 6
5 178 155 135 130 117 80
0 500 1000 1500 2000 2500 3000
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Table 1a. Breast Cancer Cases According to Body Mass Index and other Demographic and Clinical Characteristics

Stages I, II, and III Breast Cancer Patients from the POC-BP Study (2004)

Patient Characteristic	No.[1] (N = 5,394)	Weighted %	BMI (kg/m^2) Mean	SE	p-value[2]
BMI Category (kg/m^2)					
< 18.5	78	1.5			
18.5-24.9	1622	32.6			
25-29.9	1597	30.3			
30-34.9	1128	19.8			
≥ 35	969	15.9			
Demographic Characteristics					
Age					
< 40	398	6.3	27.9	0.4	
40-49	1241	21.4	28.5	0.2	
50-59	1427	26.7	29.2	0.2	< 0.001
60-69	1119	21.5	29.5	0.2	
70-79	823	16.3	28.0	0.2	
≥ 80	386	7.9	26.5	0.3	
Race					
White, non-Hispanic	3045	75.6	27.9	0.1	
Black, non-Hispanic	1486	13.9	31.0	0.2	
AI/AN, non-Hispanic	43	0.3	29.4	1.7	< 0.001
API, non-Hispanic	315	3.6	24.4	0.5	
Hispanic	502	6.6	28.6	0.3	
Insurance					
Private	3238	62.9	27.9	0.1	
Medicare/other public	1083	21.2	28.3	0.2	
Medicaid	757	10.3	29.8	0.3	< 0.001
None	158	2.0	28.4	0.6	
Unknown	158	3.7	28.7	0.5	
Census-tract education					
Higher	3286	69.2	27.8	0.1	< 0.001
Lower	2093	30.8	29.2	0.2	
Census-tract poverty					
Lower	4065	82.8	29.1	0.2	< 0.001
Higher	1314	17.2	28.1	0.1	
Urbanicity					
Urban	2773	52.5	28.0	0.1	
Urban/Rural mixed	1856	34.9	28.4	0.2	0.01
Rural	751	12.7	28.9	0.3	
Registry (State)					
1	600	17.2	28.7	0.2	
2	490	9.2	28.2	0.3	
3	577	11.2	28.5	0.3	
4	321	9.2	27.7	0.3	< 0.001
5	983	8.7	29.2	0.3	
6	1298	18.6	28.7	0.2	
7	1125	25.9	27.5	0.2	

continued in Table 1b

Abbreviations: AI/AN, American Indian/Alaska Native; API, Asian/Pacific Islander

1. Totals may not add up to 5,394 due to missing values for some variables.
2. P-values from general linear models comparing means between categories adjusted for age.

Table 1b. Breast Cancer Cases According to Body Mass Index and other Demographic and Clinical Characteristics, continued

Stages I, II, and III Breast Cancer Patients from the POC-BP Study (2004)

Patient Characteristic	No.[1] (N = 5,394)	Weighted %	BMI (kg/m^2) Mean	SE	p-value[2]
Clinical Characteristics					
Tumor Stage (AJCC)					
I	2509	48.4	27.6	0.1	
II	2067	37.6	28.5	0.2	< 0.001
III	818	14.0	29.4	0.2	
Lymph Nodes					
Any positive	1920	33.9	28.9	0.2	
All negative	3234	61.6	28.0	0.1	< 0.001
Unknown	240	4.5	27.2	0.4	
Tumor Size					
≤ 0.5 cm	451	8.8	27.7	0.3	
0.51 - 1 cm	847	16.2	27.3	0.2	
1.01 - 2 cm	1616	30.5	28.0	0.2	< 0.001
2.01 - 5 cm	2011	37.1	28.6	0.2	
> 5 cm	410	6.3	29.5	0.4	
Unknown	59	1.2	31.1	0.8	
Histologic Type					
Ductal	3978	73.2	28.3	0.1	
Lobular	373	7.3	28.4	0.3	0.02
Mixed ductal/lobular	348	7.3	27.1	0.3	
Other	695	12.3	28.3	0.3	
Grade					
Well differentiated	943	19.0	27.6	0.2	
Moderately differentiated	2051	39.0	28.2	0.2	
Poorly differentiated	2036	35.8	28.5	0.2	0.07
Undifferentiated	62	1.0	28.6	0.9	
Unknown/other	302	5.1	28.6	0.4	
Hormone Receptor Status					
ER+ and/or PR+	3846	73.0	28.4	0.1	
ER- and PR-	1316	22.5	27.9	0.2	0.13
Unknown	232	4.5	27.7	0.4	
HER2 Receptor Status					
HER2+	1907	34.4	28.2	0.2	
HER2-	2647	49.7	28.3	0.1	0.93
Unknown	840	15.9	28.3	0.2	
Comorbidity					
None	2420	45.5	26.4	0.1	
Mild	2440	44.0	30.0	0.1	< 0.001
Moderate	373	7.4	29.3	0.3	
Severe	161	3.1	28.9	0.5	

Abbreviations: ER+, estrogen receptor-positive; ER-, estrogen receptor-negative; PR+, progesterone receptor-positive; PR-, progesterone receptor-negative; HER2+, human epidermal growth factor 2 receptor-positive; HER2-, human epidermal growth factor 2 receptor-negative.

1. Totals may not add up to 5,394 due to missing values for some variables.
2. P-values from general linear models comparing means between categories adjusted for age.

Table 2. Vital status of women with stage I, II, or III breast cancer five to eight years after diagnosis and five-year mortality according to American Joint Commission on Cancer (AJCC) stage

	Lost to Follow-Up, N (%)	Alive, N (%)	Deceased, N (%)
5 years from diagnosis	0 (0)	4630 (85.8)	764 (14.2)
6 years from diagnosis	1429 (26.5)	3052 (56.6)	913 (16.9)
7 years from diagnosis	3345 (62.0)	1040 (19.3)	1009 (18.7)
8 years from diagnosis	4356 (80.8)	5 (0.1)	1033 (19.2)

	Five Year All-Cause Mortality		**Five Year Breast Cancer-Specific Mortality**	
	N	%	N	%
Overall	764	14.2	514	9.5
Stage I	203	8.1	69	2.8
Stage II	288	13.9	194	9.4
Stage III	273	33.4	251	30.7

Table 3. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for All-Cause Mortality and Breast Cancer-Specific Mortality According to Body Mass Index

Patient Characteristic	All-Cause Mortality			Breast Cancer-Specific Mortality		
	HR	95% CI	p-value for trend	HR	95% CI	p-value for trend
Model Adjusting for Age, Tumor Stage, and Other Clinical and Demographic Characteristics[1]						
Body Mass Index (kg/m^2)						
< 18.5	1.31	0.80 - 2.15		**0.33**	0.12 - 0.93	
18.5-24.9	1 (ref)			1 (ref)		
25-29.9	0.82	0.67 - 1.01		0.87	0.4 - 1.19	
30-34.9	**0.75**	0.59 - 0.95		0.94	0.68 - 1.30	
≥35	0.85	0.67 - 1.08		0.93	0.64 - 1.35	
per 5 kg/m2 Δ	**0.93** (0.87 - 0.95)		**0.02**	0.98 (0.94 - 1.02)		0.42
Age at Diagnosis (years)	1.04	1.03 - 1.05	< 0.001	1.00	0.99 - 1.01	0.91
Tumor Stage (AJCC)						
I	1 (ref)		< 0.001	1 (ref)		< 0.001
II	1.62	1.34 - 1.95		3.36	2.33 - 4.86	
III	3.94	3.19 - 4.86		12.23	8.57 - 17.46	

Abbreviations: AJCC, American Joint Commission on Cancer

1. Model 2 adjusted for age, tumor stage, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status, and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity.

Table 4. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for All-Cause Mortality According to Body Mass Index, Stratified by Age at Time of Diagnosis[1]

		All-Cause Mortality[2]		
	N	HR	95% CI	p-value for trend
Under 50 Years of Age (N = 1637)				
Body Mass Index (kg/m^2)				
< 18.5	26	**0.10**	0.01 - 0.85	
18.5-24.9	585	1 (ref)		
25-29.9	408	0.94	0.59 - 1.51	0.79
30-34.9	306	0.89	0.54 - 1.46	
≥35	312	1.04	0.63 - 1.73	
50 to 69 Years of Age (N = 2541)				
Body Mass Index (kg/m^2)				
< 18.5	26	1.05	0.36 - 3.04	
18.5-24.9	651	1 (ref)		
25-29.9	773	0.82	0.57 - 1.19	0.30
30-34.9	581	0.77	0.52 - 1.13	
≥35	510	0.84	0.56 - 1.28	
70 Years of Age or Older (N = 1201)				
Body Mass Index (kg/m^2)				
< 18.5	25	**1.92**	1.11 - 3.34	
18.5-24.9	381	1 (ref)		
25-29.9	414	0.84	0.63 - 1.14	
30-34.9	239	0.73	0.51 - 1.05	
≥35	142	0.78	0.52 - 1.17	
per 5 kg/m2 Δ		**0.85**	0.75 - 0.95	**0.01**

1. p-value for interaction term (age*BMI) = 0.01.
2. Models adjusted for AJCC stage, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status, and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity.

Table 5. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for All-Cause Mortality According to Body Mass Index, Stratified by AJCC Stage at Diagnosis[1]

		All-Cause Mortality[2]		
	N	HR	95% CI	p-value for trend
Stage I (N = 2504)				
Body Mass Index (kg/m^2)				
< 18.5	40	**1.95**	1.03 - 3.69	
18.5-24.9	807	1 (ref)		
25-29.9	780	0.85	0.60 - 1.21	0.40
30-34.9	495	0.71	0.48 - 1.06	
≥35	382	1.16	0.74 - 1.83	
Stage II (N = 2060)				
Body Mass Index (kg/m^2)				
< 18.5	27	0.90	0.35 - 2.29	
18.5-24.9	594	1 (ref)		
25-29.9	584	0.77	0.55 - 1.08	0.51
30-34.9	448	**0.66**	0.45 - 0.96	
≥35	407	0.84	0.58 - 1.23	
Stage III (N = 815)				
Body Mass Index (kg/m^2)				
< 18.5	10	0.63	0.24 - 1.70	
18.5-24.9	216	1 (ref)		
25-29.9	231	0.73	0.49 - 1.08	0.11
30-34.9	183	0.86	0.56 - 1.30	
≥35	175	0.7	0.44 - 1.11	

1. A significant interaction between BMI and AJCC stage was not found (p = 0.83); stratified analysis was conducted descriptively.
2. All models adjusted for age, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status, and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity.

Table 6. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Breast Cancer-Specific Mortality According to Body Mass Index, Stratified by AJCC stage at Diagnosis[1]

		Breast Cancer-Specific Mortality[2]		
	N	HR	95% CI	p-value for trend
Stage I (N = 2414)				
Body Mass Index (kg/m^2)				
< 18.5	39	2.33	0.54 - 10.08	
18.5-24.9	788	1 (ref)		
25-29.9	739	1.47	0.67 - 3.20	
30-34.9	475	1.06	0.45 - 2.52	
≥35	373	**4.74**	1.78 - 12.59	
per 5 kg/m2 Δ		**1.38** (1.22 - 1.55)		**0.004**
Stage II (N = 2060)				
Body Mass Index (kg/m^2)				
< 18.5	27	not estimable		
18.5-24.9	594	1 (ref)		
25-29.9	584	0.88	0.53 - 1.47	0.51
30-34.9	448	0.80	0.47 - 1.35	
≥35	407	0.87	0.48 - 1.58	
Stage III (N = 815)				
Body Mass Index (kg/m^2)				
< 18.5	10	0.32	0.06 - 1.84	
18.5-24.9	216	1 (ref)		
25-29.9	231	0.74	0.47 - 1.17	0.20
30-34.9	183	0.97	0.62 - 1.54	
≥35	175	0.69	0.41 - 1.17	

1. p-value for interaction term (stage*BMI) = 0.04.
2. All models adjusted for age, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status, and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity.

CHAPTER FIVE: PAPER 2 – Obesity and Guideline-Concordant Treatment for Locoregional Breast Cancer

Abstract

Purpose:

Breast cancer patients who are obese have higher average mortality than non-obese breast cancer patients. Hypothesizing that poorer outcomes in obese patients may be partially attributable to a lower likelihood of receiving adequate treatment for their breast cancer, we examined whether breast cancer patients with higher body mass index (BMI) were less likely to receive care consistent with National Comprehensive Cancer Network Guidelines.

Patients and Methods:

Stage I, II, and III breast cancer cases diagnosed in 2004 (n = 5361) were identified from a National Program of Cancer Registries-funded Patterns of Care study. Differences in treatment according to BMI category were investigated using adjusted logistic regression models in the study population as a whole as well as in subgroups defined according to age or AJCC stage where an interaction was found to exist between BMI and one of these characteristics in predicting treatment. Tests for interactions according to race and tumor registry were also conducted.

Results:

Higher BMI was associated with greater odds of receiving overall guideline-concordant therapy, defined as treatment guideline-concordant in all domains of post-surgical therapy (p-value for

trend = 0.01; OR for 5 kg/m^2 difference in BMI = 1.09, 95% CI 1.02 to 1.15). Within specific treatment domains, BMI was not associated with receipt of guideline treatment in the general study population. However, among some sub-groups, some relationships were found between BMI and guideline-concordant therapy in certain domains. Specifically, women with greater BMI were more likely to have lymph nodes evaluated as recommended by guidelines; in age-stratified analyses this result was limited to women aged ≥70 years. Among women with Stage III (non-T3N1M0) disease, greater BMI was associated with higher odds of guideline-concordant hormonal therapy. Among women with Stage I disease, odds of receiving guideline-concordant adjuvant chemotherapy were lower among women with higher BMI.

Conclusion:

Contrary to our hypothesis, odds of overall guideline concordant systemic therapy were moderately higher among women with greater BMI. In the sample as a whole, women with higher BMI were not more or less likely to receive guideline-concordant treatment within any specific treatment domain. The pattern of lower odds of guideline chemotherapy within the subgroup of women with Stage I disease is an important finding given the high incidence and generally good prognosis of early stage breast cancer, and future research combining assessment of appropriate adjuvant chemotherapy initiation with appropriate chemotherapy dose would be valuable. Conversely, higher BMI was associated with greater odds of guideline intra-operative lymph node sampling among older women, and with greater odds of guideline hormonal therapy among the women with the most advanced disease. In older adults, higher BMI can be correlated with better functional status, which could explain in part the positive association between BMI

and lymph node sampling in older women; factors potentially driving the positive association between being in the highest category of BMI examined and likelihood of receiving guideline hormonal therapy are less apparent. Further research describing how multiple factors, including treatment patterns, influence outcomes for obese breast cancer patients may identify areas where changes in practice can reduce disease burden and mortality.

Introduction

As the prevalence of obesity increases, its role in breast cancer risk and outcomes is of greater public health importance. Substantial evidence suggests not only that obesity is associated with 30 to 50 percent higher risk of breast cancer among postmenopausal women,[1] but also that obese breast cancer patients of all ages have higher rates of disease recurrence and mortality.[2-31] Poor outcomes among obese patients likely reflect multiple factors. Obesity is associated with physiological risk factors for breast cancer mortality, including greater inflammation and endocrine factors thought to promote tumor progression.[48] Obese patients may present with a more advanced stage due to delayed diagnoses.[48,55,57] In addition to these factors, some evidence suggests obese breast cancer patients may have a higher likelihood of receiving inadequate treatment.[62,63,69,71-73,81]

Much of the research on obesity and breast cancer treatment has focused on dose intensity of systemic therapies. Some studies indicate that obese patients may have been receiving inadequate doses of aromatase inhibitors,[25,81] and furthermore, several studies have found suboptimal adjuvant chemotherapy dosing among obese breast cancer patients,[62,63,69,71-73] despite evidence that dosing based on actual, rather than "ideal" or "adjusted," body weight increases

efficacy without higher incidence of toxicity-related adverse events, leading to inclusion of this recommendation in guidelines.[62,69,71,74-78] The possibility that other disparities in treatment related to obesity may exist – for example, differences in the initiation of appropriate post-surgical treatments – motivated our investigation of body size and the likelihood of receiving treatment in accordance with evidence-based clinical guidelines.

There has been little research on the relation between obesity and patterns of care as measured against widely disseminated clinical practice guidelines.[79,82] In this analysis, we used data from a large, comprehensive study focusing on patterns of care to examine whether breast cancer patients with higher body mass index were less likely to receive care consistent with the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology.

Data and Methods

Data Sources

This study used data from the National Program of Cancer Registries Breast and Prostate Cancer Data Quality and Patterns of Care Study (POC-BP) to examine whether use of guideline-concordant care differs by patient body mass index (BMI), controlling for patient and health system factors.[101] The POC-BP data set comprised breast and prostate cancer cases diagnosed in 2004 selected from population-based cancer registries in California, Georgia, Kentucky, Louisiana, Minnesota, North Carolina, and Wisconsin. Registry information was supplemented with information abstracted by certified tumor registrars from medical records at hospitals and physicians' offices.

Eligibility Criteria

Women 20 years or older diagnosed in 2004 with primary breast cancer (other than by autopsy or death certificate) were eligible for POC-BP if they had no previous diagnoses of *in situ* or invasive breast cancer, other reportable cancers, Paget's disease, Kaposi's sarcoma, or lymphoma. Cases were selected from registries using random sampling stratified by race/ethnicity, as well as Appalachian/non-Appalachian region in North Carolina and Kentucky, facility type and volume in Wisconsin, and urban-rural status in Georgia.[66,101]

A total of 6,967 patients with Stage I, II, or III disease were identified. Women who did not receive any surgery for their breast cancer (n = 105) were excluded from analyses. Women with unknown BMI (n = 1462) were also excluded (this paper's Discussion section and Appendix C address some potential issues related to non-random missingness of BMI). Finally, women with certain cancer diagnoses not considered reportable by the tumor registries, including some skin carcinomas, carcinoma *in situ* of the cervix, borderline ovarian cancers, benign brain tumors, and lymphohematopoietic malignancies diagnosed before 2001 (n = 39), were excluded from the analytic data set, leaving 5,361 cases.

Definitions of Guideline Concordant Care by Treatment Modality

Guideline concordant care was identified based on NCCN Clinical Practice Guidelines in Oncology version 1.2003,[103] the version applicable when these cases were diagnosed.

Primary Therapy

Surgery with sampling and examination of regional lymph nodes was recommended by guidelines for all women with invasive cancer. Therefore, failure to sample at least one lymph node was defined as non-concordant.

The guidelines for post-surgical radiation therapy make recommendations for receipt or nonreceipt (or optional receipt) of radiation according to the disease stage, type of surgery received, and characteristics of the tumor before surgery (see Fig. 1). Any patients for whom the guidelines recommended radiation therapy who did not receive this therapy, and any patients for whom the guidelines specified that radiation therapy should not be given who did receive this treatment, were considered to have received non-guideline-concordant treatment (under-treatment and over-treatment, respectively). Women for whom the guidelines indicated radiation therapy was optional were considered to have received guideline-concordant treatment in this domain whether or not they received radiation therapy as part of their treatment course.

Adjuvant Therapies

Adjuvant chemotherapy was recommended by guidelines depending on tumor characteristics (see Fig. 2). Patients who were 70 or older (N=1161) and/or had certain rare histologic tumor types (N = 774) were not covered by the NCCN guidelines on adjuvant chemotherapy and were therefore considered to have received guideline treatment regardless of whether adjuvant chemotherapy was received. In addition, NCCN guidelines for systemic therapies recommend that physicians "consider adjuvant therapy" for patients with certain tumor characteristics, including mid-range size and/or colloid or tubular histology; since there was no single guideline-concordant treatment for patients with these tumor characteristics, they were also all considered to have received guideline care (N=579). Non-concordant treatment included non-receipt of chemotherapy among patients for whom guidelines recommended it (under-treatment) and chemotherapy receipt among patients for whom none was recommended (over-treatment).

Among patients who did receive guideline-concordant adjuvant chemotherapy, the specific regimen received was considered guideline-concordant if listed as an NCCN guideline-approved agent, or if received as part of a clinical trial.

Hormonal therapy, defined as orally-administered tamoxifen or aromatase inhibitors (AIs), was recommended by the NCCN guidelines for all women with hormone receptor-positive (estrogen receptor (ER)- and/or progesterone receptor (PR)-positive) tumors. Nonreceipt of hormonal therapy among women with ER+ and/or PR+ tumors was considered non-concordant (under-treatment), as was receipt of hormonal therapy among women with ER- and PR-negative tumors (over-treatment).

"Overall guideline-concordant treatment" was defined as guideline concordance in all of the post-surgical treatment domains (radiation and the three adjuvant systemic therapy components).

Clinical and Demographic Covariates

Patient age was determined at time of diagnosis. Race/ethnicity information was obtained from patients' medical records, and from information found in Indian Health Services patient registration. When Hispanic origin was unclear, an identification algorithm developed by the North American Association of Central Cancer Registries was used.[112]

Insurance status was categorized as private, Medicare or other public insurance only, Medicaid, uninsured, and unknown. The "private" category included patients with Medicare plus private supplemental insurance. Women who were dual-eligible for Medicare and Medicaid were grouped in the Medicaid category.

Education and socioeconomic status were based on census tract information for the patient's place of residence. Patients were categorized as living in a higher poverty (≥ 20% of residents

below the federal poverty level) or lower poverty area, and as living in a lower education (≥ 25% of adults ≥ 25 years of age with less than high-school education) or higher education area. Residential areas were described as 100% urban, mixed, or 100% rural, using the 2000 U.S. Census Bureau's urban and rural criteria.

A modification of the Piccirillo (ACE-27) comorbidity index[105] considered each of 25 conditions (26 from the Piccirillo comorbidity index, minus obesity and not including the index breast cancer) and assigned a 1-3 score for "level of decompensation," where 1 is Mild, 2 is Moderate, and 3 is Severe. The overall comorbidity score was either based on the single highest-ranking condition or assigned a value of grade 3 if the highest-ranking ailments are grade 2 but they occurred in different organ systems.

Statistical Analysis

The analysis compared treatment of patients across BMI categories, as defined by the World Health Organization ("underweight" if BMI<18.5 kg/m^2, "normal" if BMI was 18.5-24.9 kg/m^2, "overweight" if BMI was 25.0-29.9 kg/m^2, "obese" if BMI was 30.0-34.9 kg/m^2, and "very obese" if BMI≥35 kg/m^2).[113] Odds ratios (OR) and 95% confidence intervals (CI) for receipt of versus nonreceipt of the guideline-concordant option for each treatment were estimated using multivariable logistic regression. Covariates were chosen *a priori* because of a known or potential relationship with BMI and with treatment choices, and included race/ethnicity, health insurance, education, socioeconomic status, tumor registry, urban/rural residence, tumor size, lymph node status, tumor grade, hormone receptor status, and comorbidities. We used sampling weights to account for the POC-BP sampling design. The regression models also accounted for clustering by treatment facility, using robust standard errors incorporating information on the

number of cases treated at each facility. We calculated p-values for trend for each model, representing the extent to which a linear trend relating BMI to treatment receipt was present, by running a second version of the model in which BMI was represented by a continuous variable. Based on findings in the existing literature, we tested for interactions according to age; race or ethnicity; and tumor registry (geographic area). We also tested for interactions according to tumor stage or stage category; the latter interaction test compared the BMI-treatment association among women with tumors staged as I, II, or III with T3N1M0 pathologic staging (these Stage III tumors are grouped in with Stage I and II in guidelines for most treatment domains) to the association among women with Stage III, non-T3N1M0 disease.

Results

Table 1 shows BMI according to demographic and clinical characteristics of the study population. The mean BMI was 29.1 kg/m^2 and the median, 28.0 kg/m^2. Most women (69.5%) were between the ages of 40 and 70 at the time of diagnosis, with 6.3% under age 40 and 24.2% age 70 or older. Age at diagnosis was associated with BMI ($p < 0.001$); women in the middle age categories (age 50-69) had higher mean BMI (29.2-29.5) compared to younger women (mean BMI = 28.5 among women age 40-49 and 27.9 among women under 40) and to older women (mean BMI = 28.1 among women age 70-79 and 26.5 among women age 80 or older). Age-adjusted analyses were conducted to examine associations between BMI and other demographic and clinical variables.

Most women (75.5%) were white. Race/ethnicity was associated with BMI ($p < 0.001$), with black women having the highest mean BMI (31.0 kg/m^2) and Asian or Pacific Islander women

having the lowest (24.4 kg/m^2). The majority of women (62.9%) were privately insured. Insurance type and BMI were associated ($p < 0.001$); those insured by Medicaid had the highest average BMI, 29.8 kg/m^2, as compared to 27.9 kg/m^2 among those with private insurance. 82.7% of the women lived in low-poverty areas and 69.3% in high-education areas. Women in higher-education census tracts and in lower-poverty census tracts tended to have lower BMI ($p < 0.001$ for both). Half of the women (52.5%) lived in urban areas. Women in rural areas had higher mean BMI (28.9 kg/m^2), compared to those living in urban areas (mean BMI, 28.0 kg/m^2) or mixed urban and rural regions.

AJCC stage at diagnosis was either I or II for most women (48.4% stage I, 37.6% stage II, with 14% being stage III). The majority of tumors (83.8%) were between 0.5 and 5 cm in diameter. Higher AJCC stage and larger tumor size were associated with higher BMI. The majority of cases had well- or moderately-differentiated tumors (58.1%), and negative lymph nodes (61%). Having one or more positive lymph nodes was associated with higher BMI ($p < 0.001$); higher tumor grade showed a borderline positive association with higher BMI ($p = 0.07$). 73% of tumors were hormone receptor-positive. Hormone receptor status was not associated with BMI ($p = 0.19$). Approximately half (49.8%) of tumors were human epidermal growth factor 2 (HER2) receptor-negative. HER2 receptor status was not associated with BMI ($p = 0.94$). Most patients (89.8%) had either no comorbid conditions or mild comorbidity. Comorbidity burden was associated with BMI ($p < 0.001$), although not in a linear fashion. While the lowest mean BMI (26.4) was found among women with a comorbidity score of 0 (no comorbid conditions), the highest mean BMI was found among women with a score of 1 (mild comorbidity).

Table 2 provides a descriptive summary of the types of treatments women with stage I, II, and III tumors received. Over half of women (58%) received radiation as part of their first course of therapy, and just over half of women (53%) received adjuvant chemotherapy. The proportion of women receiving hormonal therapy (tamoxifen or AIs) was also just over half (53%). Most women (59%) received therapy in two or more of the therapeutic domains. 12% of women did not receive any post-surgical treatments.

Receipt of Guideline-Concordant Treatment **(Table 3)**

Overall, 95.7% of women had one or more lymph nodes sampled during their surgery as guidelines recommend. Results of the logistic regression model suggested that patients with higher BMI had higher odds of having at least one lymph node sampled: patients with a BMI of 30-34.9 kg/m^2 had the highest odds of having lymph nodes sampled (OR = 2.01, 95% CI 1.16 to 3.48, compared to patients in the reference category of BMI 18.5-24.9 kg/m^2), followed by patients with a BMI of 25-29.9 kg/m^2 (OR = 1.86, 95% CI 1.19 to 2.91) The p-value for the test of overall linear trend, from the model using continuous BMI, was 0.12 (OR for a difference of 5 kg/m^2 = 1.15, 95% CI, 0.97 to 1.38). There was a suggestion that the association between BMI and lymph node evaluation varied by age (p-value for interaction term = 0.09). Table D1 in Appendix D presents stratified results for separate models examining BMI and lymph node sampling according to age category. Among women who were under age 70, the association between BMI category and lymph node sampling appeared to be null, but among patients age 70 and older, women with higher BMI had higher odds of having lymph nodes sampled (OR for BMI of 25-29.9 kg/m^2 compared to BMI of 18.5-24.9 kg/m^2 = 2.50, 95% CI 1.43 to 4.39; OR for

BMI of 30-34.9 kg/m^2 = 2.47, 95% CI 1.22 to 5.02; and OR for BMI ≥35 kg/m^2=2.25, 95% CI 1.08 to 4.72; p-value for linear trend=0.01, not shown).

Overall, 83% of women received guideline-concordant adjuvant radiation therapy. BMI was not associated with odds of guideline-concordant radiation therapy.

Overall, 84.8% of women received guideline-concordant adjuvant chemotherapy. About 0.7% of women were over-treated and 14.5% were under-treated. Women with BMI of 25-29.9, and potentially women with BMI of 30-34.9, appeared to have lower odds of receipt of guideline-concordant adjuvant chemotherapy compared to women in the reference category (OR for BMI of 25-29.9 kg/m^2 compared to BMI of 18.5-24.9 kg/m^2 = 0.68, 95% CI 0.53 to 0.88 and OR for BMI of 30-34.9 kg/m^2 compared to 18.5-24.9 kg/m^2 = 0.75, with 95% CI 0.55-1.03), although the overall trend was far from achieving statistical significance (p = 0.49). When over-treatment and under-treatment were considered separately, BMI was found not to be associated with either (not shown). An interaction was observed between BMI and AJCC stage (p = 0.004 for significance of interaction term) with regard to adjuvant chemotherapy; among women with Stage II or Stage III disease, a null association between BMI and guideline-concordant treatment was observed, but among women with Stage I disease, women in higher BMI categories had lower odds of receiving guideline-concordant treatment compared to women in the reference category (OR for BMI ≥ 35 kg/m^2 = 0.51, 95% CI 0.31 to 0.86; p-value for trend = 0.01, not shown). Table D2 in Appendix D shows these results. There was a suggestion, not reaching statistical significance, that the association between BMI and receipt of guideline-concordant adjuvant chemotherapy might differ according to age, even among women under age 70, who

were not automatically considered to have received guideline chemotherapy (p-value for interaction term = 0.06 among women age 69 or younger at diagnosis).

Among women who received guideline-concordant chemotherapy, 73.6% received a regimen that was concordant with guidelines. BMI was not associated with odds of receiving a guideline-concordant regimen.

Overall, 79.5% of women received guideline-concordant hormonal therapy consisting of tamoxifen or aromatase inhibitors; 19.5% percent of women were under-treated and 1% were over-treated. In the sample as a whole, BMI category was not associated with receipt of guideline-concordant hormonal therapy, nor specifically with over-treatment or under-treatment. However, a borderline significant interaction according to tumor stage group was found (p = 0.09), and stage group-stratified analysis revealed that BMI was associated with receipt of guideline hormonal therapy among women with Stage III, non-T3N1M0 disease. Among these women with more advanced disease, greater BMI was significantly associated with greater odds of receiving guideline-concordant hormonal therapy (OR for BMI $\geq$ 35 kg/m^2 = 2.58, 95% CI 1.12 to 5.98, and p-value for test of overall linear trend = 0.01, with OR of 1.25 for a difference of 5 kg/m^2), while for women with less advanced tumors at diagnosis, the relationship between BMI and guideline hormonal therapy appeared to be null (see Table D3 in Appendix D).

Fewer than half of women (42.6%) of women received treatment that was overall guideline-concordant. Higher BMI was associated with greater odds of overall guideline-concordant treatment (p-value for trend = 0.01; OR for 5 kg/m^2 difference in BMI = 1.09, 95% CI 1.02 to 1.15). The proportion of women receiving overall guideline-concordant treatment differed notably by tumor registry (from 31.5% to 54.4%), but there was no apparent interaction between

BMI and tumor registry with regard to likelihood of overall guideline-concordant therapy (p = 0.50). The relationship between BMI and receipt of overall guideline-concordant treatment also did not appear to differ according to AJCC stage (I, II, or III) or tumor stage group (I, II, and IIIT3N1M0 versus stage III, not T3N1M0); p-values for the interaction terms were 0.41 and 0.83, respectively.

We explored whether any associations between BMI and treatment might vary according to age, race, or tumor registry. Aside from the apparent interactions noted above, between BMI and age in lymph node removal and the potential interaction between BMI and age in receipt of guideline-concordant adjuvant chemotherapy, no significant interactions according to age were observed, and no significant interactions according to race or tumor registry were found (data not shown).

Discussion

This study aimed to identify differences in breast cancer treatment by BMI category, using NCCN oncology practice guidelines from 2003 as a standard of care measure. Recognizing that the "ideal" situation might not include perfect adherence to these guidelines, given the important role for clinical judgment and consideration of patient preference, we chose this method for its utility as a means of quantifying process outcomes in a manner comparable with other studies.

Overall, the proportion of patients receiving guideline-concordant therapy was for the most part consistent with prevailing knowledge. Literature on rates of guideline-concordant lymph node surgery is limited; however, Landercasper and colleagues reported a rate of 97%, a value very similar to that found in our study (96%). [114] We found that 83% of women received guideline-concordant radiation therapy, a proportion only slightly higher than the 77% reported

by Landercasper et al;[114] the proportion we found was, in contrast, lower than that reported by Punglia et al (92%), but it should be noted these authors were reporting on patterns of care among women with early stage disease treated at NCCN centers. The proportion of patients receiving guideline-concordant chemotherapy (85%) fell toward the higher end of a wider range of estimates observed in other studies (63% in a single-center study by Landercasper et al; 65% in a study by Wu et al; 90% in a study by Neugut and colleagues).[66,89,114] Findings on receipt of hormone therapy among women for whom this treatment was recommended also show a wide range of estimates for the proportion receiving appropriate therapy. Our finding on the proportion of women receiving guideline-concordant hormonal therapy (79.5%) was similar to the proportion reported by Bloom et al (80% among women diagnosed in 1995-1999 in the Northeastern United States),[115] as well as that found by Kimmick et al (76%) among women diagnosed in 2006-2008.[116] It was somewhat higher than the 64% reported by Guadagnoli et al in 1998, although these authors measured adherence only among postmenopausal women,[117] and substantially higher than the 53% reported by Freedman and colleagues using data from women diagnosed in 1998-2005,[118] but it was low compared to the 89% of women diagnosed in 2005-2007 who initiated appropriate hormonal therapy as reported by Friese and colleagues.[119] These differences could reflect changes in practice over time or, perhaps more likely, geographic variation.

Comparing the proportion of women receiving guideline-concordant treatment across BMI categories using models adjusting for demographic and clinical characteristics resulted in findings that, for the most part, were contrary to our hypotheses regarding the relationship between BMI and guideline treatment. In particular, the odds of receiving overall guideline-

concordant post-surgical therapy were moderately higher among women who had higher BMI at the time of diagnosis. This was the only finding regarding BMI and treatment received that applied to the whole group of women examined. Lymph node sampling, as recommended by guidelines, as well as appropriate receipt of hormonal therapy, were also found to be more common among women with higher BMI, but this was true only in certain subcategories.

The positive association between BMI and likelihood of lymph node sampling was unexpected, but the fact that it was seen only among older adults may partially explain this finding, as body mass in older adults may correlate with functional status and overall health, which would tend to move the risk-benefit ratio to support lymph node dissection. The association between higher BMI and likelihood of guideline-concordant hormonal therapy among women with stage III, non-T3N1M0 disease is harder to explain. Among this group, women in the highest BMI category were found to have substantially higher odds of receiving guideline hormonal therapy compared to women in the "normal"-weight reference category, whereas the difference in odds between other BMI categories was not significant (or not estimable, in the case of women with BMI < 18.5 kg/m^2, due to small numbers). Although women with Stage III, non-T3N1M0 disease constituted a small proportion of the study population (700 women), it is notable that these most-obese women would have such elevated likelihood of receiving guideline treatment in this domain.

In contrast with the findings regarding lymph node sampling and hormonal therapy, we did find that among the subcategory of women with Stage I disease, women with higher BMI were less likely to receive guideline-concordant treatment in the domain of adjuvant chemotherapy. Given the generally very good prognosis among women with tumors diagnosed as Stage I, it will

be important in the future to continue to consider whether patients and physicians under-treat women in this category, and what affects decision-making regarding the risk-benefit ratio in this generally lower-risk group. It should be noted, also, that our findings reflect only the likelihood of initiation or non-initiation of adjuvant chemotherapy; there may also be systematic differences according to body size in early termination of therapy, or in chemotherapy dose, both critical issues that we were unable to assess. Thus, future research assessing determinants of both appropriate adjuvant chemotherapy initiation and appropriate chemotherapy dose would be valuable.

Interpretation of these results should consider certain limitations, in addition to those already mentioned. BMI is an imperfect measure of body shape and adiposity, and was used due to convention and to the lack of any superior measure in wide acceptance. Other limitations include: lack of education and socioeconomic status measured at the individual level; low representation, despite oversampling, of some racial/ethnic subgroups; and limited power to examine the experiences of underweight patients. In addition, our approach required exclusion of 20% of otherwise eligible patients due to missing height and/or weight. We did explore the implications of missing BMI information, comparing observed characteristics between women with and without missing BMI; findings are reported in a Supplement (Appendix B) and suggest that values for several demographic and clinical characteristics were associated with missing BMI. Beyond this incomplete data issue, incomplete medical records may have resulted in receipt of guideline-concordant treatment being slightly overestimated, although likely non-differentially; contraindications to chemotherapy or radiation may not have been captured for women with non-recorded pregnancies or certain skin disorders. Tamoxifen and aromatase

inhibitors were both counted as guideline-concordant hormonal therapy (in women for whom hormonal therapy was recommended by guidelines), although the guidelines actually considered anastrazole to be an acceptable alternative to tamoxifen for postmenopausal women but not for premenopausal women. Data on women's menopausal status were not available, preventing us from being able to make this distinction. Therefore, there may have been a slight overestimation of the percentage of women receiving guideline-concordant hormonal therapy. A significant limitation of the study was the fact that we were not able to assess chemotherapy dose intensity, which may be of greater concern than receipt or nonreceipt of systemic therapy. Finally, changes in practice and in the NCCN guidelines since 2004 could also decrease the generalizability of the findings to current practice (see Appendix E).

Using adherence to guidelines as a means of capturing variations in patterns of care has benefits and limitations. Although guidelines serve an important purpose in decreasing inappropriate variation in care, perfect compliance with guidelines is not always a reasonable or laudable goal, particularly given the importance of shared decision-making in a patient's treatment. Sets of guidelines are numerous and may offer inconsistent conclusions.[88] Nevertheless, evidence-based clinical practice guidelines disseminated and used widely and increasingly in the United States and elsewhere[87] can offer a standard for comparison of patients' treatment experience.[66,89]

This study emphasized the comparison of patients' treatment experiences according to body mass index in order to address, in part, an incompletely understood aspect of the multifactorial pathway connecting obesity and poorer outcomes after a breast cancer diagnosis. It adds to the existing evidence by drawing on a population-based sample of locoregional breast cancer

patients diagnosed in the same year and by using a widely accepted set of clinical guidelines as a framework for describing the surgical procedures, radiation, and systemic therapies patients received during first-course treatment. In research settings and elsewhere, interest is growing regarding the role of clinical guidelines and particularly in how they may be used in identifying and decreasing inappropriate variation in care.[87] This study focused on multiple process measures, each reflecting concordance or nonconcordance with clinical practice guidelines, to investigate whether different patterns of care in cancer treatment could contribute to the disparity in outcomes between obese and non-obese individuals. Broadly speaking, we found that there were not significant differences according to BMI in receipt of guideline-concordant therapy among the individual treatment domains examined, and that higher BMI was actually associated, if only modestly, with greater odds of overall guideline-concordant post-surgical treatment.

Although this study was cross-sectional and its conceptual scope descriptive, the results indicating that receipt of appropriate treatment, as captured by the measures chosen, was not less common among obese women suggests that factors other than treatment may be more important in the relationship between body size and breast cancer outcomes, a finding with continued clinical relevance as researchers attempt to understand and reduce the disparity in outcomes related to obesity. Continuing research aimed at describing the extent to which multiple factors, including treatment, may contribute to poorer outcomes among obese breast cancer patients can identify areas where changes in practice will have the most impact on disease burden and mortality.

Figures and Tables

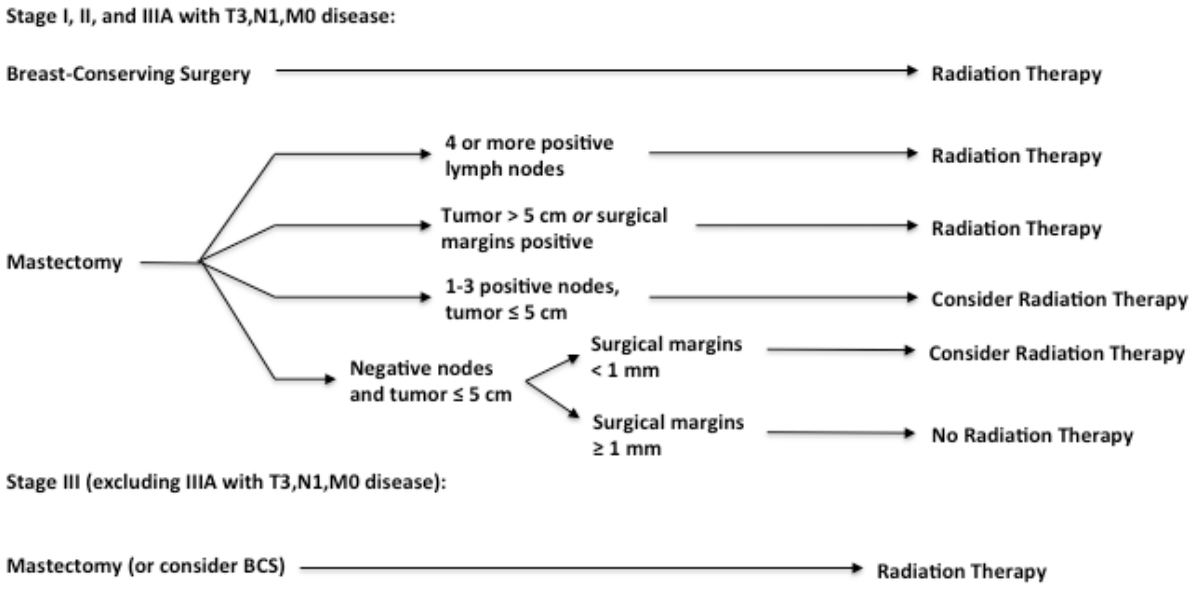

Figure 1. NCCN recommendations for radiation therapy after surgery for breast cancer.

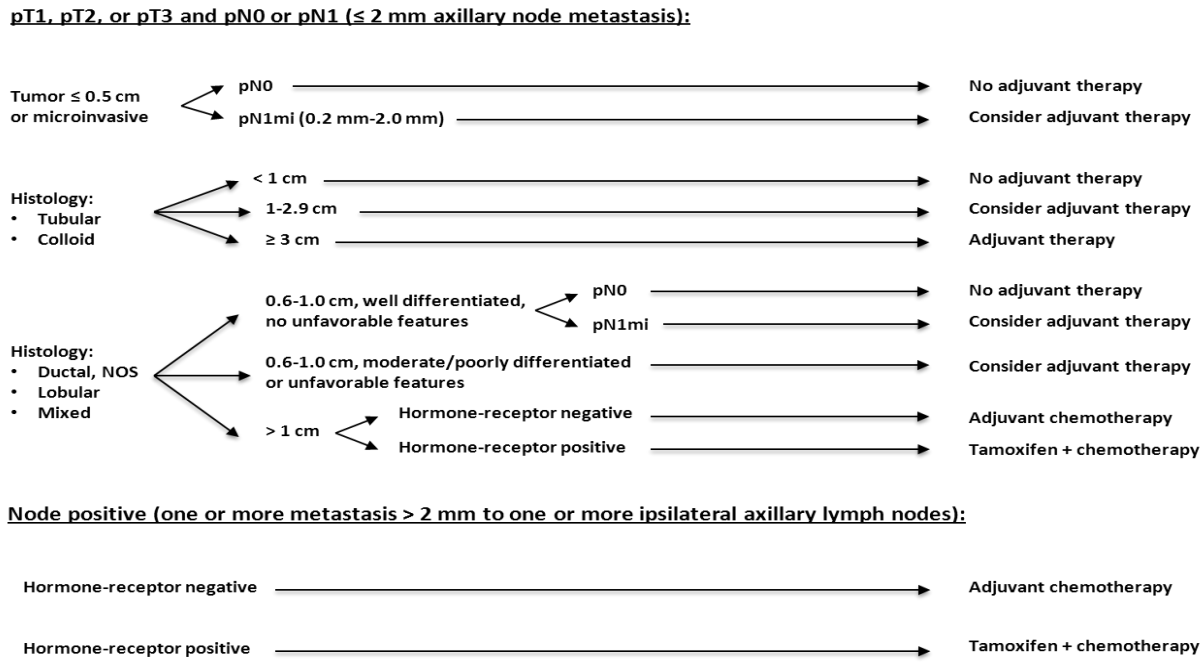

Figure 2. NCCN recommendations for adjuvant chemotherapy based on tumor characteristics in locoregional breast cancer.

Table 1a. Breast Cancer Cases According to Body Mass Index and other Demographic and Clinical Characteristics

Stages I, II, and III Breast Cancer Patients from the POC-BP Study (2004)

Patient Characteristic	No.[1] (N = 5,394)	Weighted %	BMI (kg/m^2) Mean	SE	p-value[2]
BMI Category (kg/m^2)					
< 18.5	78	1.5			
18.5-24.9	1614	32.5			
25-29.9	1589	30.3			
30-34.9	1120	19.8			
≥ 35	960	15.8			
Demographic Characteristics					
Age					
< 40	398	6.3	27.9	0.4	
40-49	1233	21.4	28.5	0.2	
50-59	1420	26.7	29.2	0.2	< 0.001
60-69	1110	21.4	29.5	0.2	
70-79	821	16.3	28.1	0.2	
≥ 80	379	7.9	26.5	0.3	
Race					
White, non-Hispanic	3015	75.5	27.9	0.1	
Black, non-Hispanic	1480	13.9	31.0	0.2	
AI/AN, non-Hispanic	43	0.3	29.4	1.7	< 0.001
API, non-Hispanic	318	3.6	24.4	0.5	
Hispanic	502	6.6	28.6	0.3	
Insurance					
Private	3219	62.9	27.9	0.1	
Medicare/other public	1074	21.2	28.3	0.2	
Medicaid	752	10.2	29.8	0.3	< 0.001
None	158	2.0	28.4	0.6	
Unknown	158	3.7	28.7	0.5	
Census-tract education					
Higher	3273	69.3	27.8	0.1	< 0.001
Lower	2073	30.7	29.2	0.2	
Census-tract poverty					
Lower	4036	82.7	28.1	0.1	< 0.001
Higher	1310	17.3	29.1	0.2	
Urbanicity					
Urban	2763	52.5	28.0	0.1	
Urban/Rural mixed	1841	34.8	28.5	0.2	0.01
Rural	743	12.7	28.9	0.3	
Registry (State)					
1	600	17.3	28.7	0.2	
2	480	9.0	28.3	0.3	
3	577	11.3	28.5	0.3	
4	321	9.2	27.7	0.3	< 0.001
5	979	8.7	29.2	0.3	
6	1277	18.4	28.7	0.2	
7	1127	26.1	27.5	0.2	

continued in Table 1b

Abbreviations: AI/AN, American Indian/Alaska Native; API, Asian/Pacific Islander

1. Totals may not add up to 5,394 due to missing values for some variables.
2. P-values from general linear models comparing means between categories adjusted for age.

Table 1b. Breast Cancer Cases According to Body Mass Index and other Demographic and Clinical Characteristics, continued

Stages I, II, and III Breast Cancer Patients from the POC-BP Study (2004)

Patient Characteristic	No.[1] (N = 5,394)	Weighted %	BMI (kg/m^2) Mean	SE	p-value[2]
Clinical Characteristics					
Tumor Stage (AJCC)					
I	2494	48.4	27.7	0.1	
II	2052	37.6	28.5	0.2	< 0.001
III	815	14.0	29.4	0.2	
Lymph Nodes					
Any positive	1907	33.8	28.9	0.2	
All negative	3218	61.7	28.0	0.1	< 0.001
Unknown	236	4.4	27.4	0.4	
Tumor Size					
≤ 0.5 cm	448	8.8	27.8	0.3	
0.51 - 1 cm	839	16.1	27.3	0.2	
1.01 - 2 cm	1608	30.5	28.0	0.2	< 0.001
2.01 - 5 cm	2000	37.1	28.6	0.2	
> 5 cm	407	6.2	29.5	0.4	
Unknown	59	1.2	31.1	0.8	
Histologic Type					
Ductal	3949	73.1	28.3	0.1	
Lobular	372	7.3	28.4	0.3	0.02
Mixed ductal/lobular	347	7.3	27.1	0.3	
Other	693	12.3	28.3	0.3	
Grade					
Well differentiated	938	19.1	27.6	0.2	
Moderately differentiated	2039	39.0	28.2	0.2	0.07
Poorly differentiated	2022	35.8	28.5	0.2	
Undifferentiated	62	1.0	28.7	0.9	
Unknown/other	300	5.2	28.7	0.4	
Hormone Receptor Status					
ER+ and/or PR+	3821	73.0	28.4	0.1	
ER- and PR-	1308	22.5	28.0	0.2	0.19
Unknown	232	4.5	27.8	0.4	
HER2 Receptor Status					
HER2+	1883	34.2	28.2	0.2	
HER2-	2639	49.8	28.3	0.1	0.94
Unknown	839	16.0	28.3	0.2	
Comorbidity					
None	2423	45.8	26.4	0.1	
Mild	2421	44.0	30.0	0.1	< 0.001
Moderate	368	7.3	29.2	0.3	
Severe	149	2.9	29.0	0.5	

Abbreviations: ER+, estrogen receptor-positive; ER-, estrogen receptor-negative; PR+, progesterone receptor-positive; PR-, progesterone receptor-negative; HER2+, human epidermal growth factor 2 receptor-positive; HER2-, human epidermal growth factor 2 receptor-negative.

1. Totals may not add up to 5,394 due to missing values for some variables.

2. P-values from general linear models comparing means between categories adjusted for age.

Table 2. Post-Surgical Treatments Received by Stages I-III Breast Cancer Patients from the POC-BP study (2004)

Treatment	No. (N = 5,361)	Weighted %
Radiation Therapy[1]		
Yes	3100	57.8
No	1974	36.8
Contraindicated	43	0.8
Refused	125	2.3
Unknown	119	2.2
Adjuvant Chemotherapy[2]		
Yes	2820	52.6
No	2153	40.2
Contraindicated	58	1.1
Refused	213	4.0
Unknown	79	1.5
Hormonal Therapy[3]		
Tamoxifen or AI	2816	52.5
Other hormonal therapy	69	1.3
No	2307	43.0
Unknown	169	3.2

Patient Characteristic	No. (N = 5,361)[4]	Weighted %
Radiation, chemotherapy, and hormonal therapy	982	18.3
Radiation and chemotherapy	855	15.9
Chemotherapy and hormonal therapy	454	8.5
Radiation and hormonal therapy	860	16.0
Radiation only	348	6.5
Chemotherapy only	457	8.5
Hormonal therapy only	486	9.1
No chemotherapy, radiation, or hormonal therapy	649	12.1
Enrolled in a clinical trial	241	4.5

Abbreviations: AI, aromatase inhibitors

1. Reasons for not receiving radiation therapy included: therapy not recommended or planned (n = 1956); therapy planned but not administered due to patient's death (n = 4); and therapy recommended but not administered, with reason unknown (n = 14). Whether radiation therapy was recommended was unknown for 47 women, while it was known to have been recommended but not known to have been performed for 72.

2. Reasons for not receiving adjuvant chemotherapy included: therapy not planned as first course treatment (n = 2140); therapy not administrated due to the patient's death (n = 1); and therapy recommended but not given, with reason unknown (n = 1). Whether adjuvant chemotherapy was recommended was unknown for 79 women, while it was known to have been recommended but not known to have been given for 38.

3. Reasons for not receiving hormonal therapy included: therapy not planned as part of first course treatment (n = 2140); therapy contraindicated due to patient risk factors (n = 40); therapy not administered before patient's death; patient refusal (n = 120); and therapy recommended but not administered, with reason unknown (n = 3)

4. Numbers do not add up to 5,361 due to missing data on receipt of one or more types of therapy (total with unknown combination = 270, 5.0%).

Table 3. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Receipt of Guideline-Concordant Treatment Among Women With Stage I-III Breast Cancer, According to BMI Category

Treatment	Overall (N and %)	BMI					
		< 18.5	18.5-24.9	25 - 29.9	30 - 34.9	≥35	p-trend
Surgery							
Lymph Nodes Sampled and Evaluated							
Yes, N	5126 (95.7)	67	1525	1521	1091	922	
No, N	231 (4.3)	11	89	66	29	36	
Odds Ratio (95% CI)[1]		0.75 (0.27 to 2.07)	1 (ref)	**1.86 (1.19 to 2.91)**	**2.01 (1.16 to 3.48)**	1.13 (0.68 to 1.88)	
per 5 kg/m^2 Δ				1.15 (0.97 to 1.38)			0.12
Radiation							
Guideline-Concordant Radiation Therapy							
Yes, N	2957 (83.0)	28	863	862	621	583	
No, N	606 (17.0)	15	180	180	115	116	
Odds Ratio (95% CI)[2]		0.30 (0.12 to 0.74)	1 (ref)	0.91 (0.66 to 1.24)	0.95 (0.64 to 1.42)	0.96 (0.64 to 1.43)	
per 5 kg/m^2 Δ				1.04 (0.94 to 1.11)			0.47
Adjuvant Therapy							
Guideline-Concordant Adjuvant Chemotherapy							
Yes, N	4421 (84.8)	64	1359	1295	919	784	
No, N	791 (15.2)	13	211	242	173	152	
Odds Ratio (95% CI)[1]		0.74 (0.38 to 1.45)	1 (ref)	**0.68** (0.53 to 0.88)	0.75 (0.55 to 1.03)	0.91 (0.65 to 1.26)	
per 5 kg/m^2 Δ				0.98 (0.91 to 1.05)			0.49

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Guideline-Concordant Regimen							
Yes, N	3796 (73.6)	55	1160	1133	786	662	
No, N	1359 (26.4%)	21	395	384	295	264	
Odds Ratio (95% CI)[1]		0.81 (0.46 to 1.43)	1 (ref)	0.85 (0.69 to 1.06)	0.90 (0.69 to 1.17)	0.92 (0.70 to 1.21)	
per 5 kg/m^2 Δ				0.99 (0.93 to 1.06)			0.80
Guideline-Concordant Hormonal Therapy							
Yes, N	3962 (79.5)	53	1166	1146	856	741	
No, N	1021 (20.5)	14	325	313	198	171	
Odds Ratio (95% CI)[3]		1.31 (0.56 to 3.09)	1 (ref)	0.88 (0.70 to 1.10)	1.12 (0.86 to 1.46)	1.21 (0.87 to 1.69)	
per 5 kg/m^2 Δ				1.06 (0.98 to 1.15)			0.14
Overall Guideline-Concordant Therapy							
Yes, N	1799 (42.6)	15	536	509	383	356	
No, N	2427 (57.4)	39	722	728	495	443	
Odds Ratio (95% CI)[1]		0.55 (0.29 to 1.04)	1 (ref)	0.87 (0.72 to 1.06)	1.11 (0.88 to 1.40)	1.14 (0.89 to 1.47)	
per 5 kg/m^2 Δ				**1.09** (1.02 - 1.15)			**0.01**

1. Model adjusted for age, tumor size, insurance type, poverty in census tract of residence, education levels in census tract of residence, urban/rural area, tumor grade, comorbidity level, and hormone receptor status. Survey sampling was stratified by tumor registry and by race/ethnicity.

2. Model adjusted for age, tumor size, insurance type, poverty in census tract of residence, education levels in census tract of residence, urban/rural area, tumor grade, comorbidity level, positive or negative lymph nodes, and hormone receptor status. Survey sampling was stratified by tumor registry and by race/ethnicity.

3. Model stratified by ER/PR status and adjusting for age, tumor size, insurance type, poverty in census tract of residence, education levels in census tract of residence, urban/rural area, tumor grade, positive or negative lymph nodes, and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity.

CHAPTER SIX: PAPER 3 – Does Guideline-Concordant Treatment Mediate the Relationship Between Obesity and Mortality After Breast Cancer Diagnosis?

Abstract

Purpose:

Mortality after a diagnosis of invasive breast cancer has been observed to be higher among women who are obese. The growing proportion of women diagnosed with breast cancer each year who are obese increases the importance of characterizing the disparity in outcomes related to women's body size and investigating potential mechanisms behind it. We examined the relationships between body mass index (BMI), cancer treatments received, and all-cause or breast cancer-specific mortality to test the hypothesis that the likelihood of treatment concordant with National Comprehensive Cancer Network (NCCN) clinical practice guidelines could be a mediator in the relationship between BMI and all-cause or breast cancer mortality among women with locoregional invasive breast cancer.

Patients and Methods:

Women diagnosed in 2004 with Stage I, II, or III breast cancer (n = 4220) were identified from a population-based, National Program of Cancer Registries-funded Patterns of Care study. Differences in overall and breast cancer-specific mortality were investigated using proportional hazards regression models. Models were then modified to include a variable indicating receipt or nonreceipt of guideline-concordant treatment after surgery (guideline radiation therapy and systemic therapies), and original and modified models were compared to assess whether receipt of guideline-concordant treatment mediated relationships between BMI and outcomes.

Results:

Women in higher BMI categories had, on average, lower hazard for overall mortality compared to women in the reference category (HR for BMI of 30-34.9 kg/m^2 compared to BMI of 18.5-24.9 = 0.77, 95% CI, 0.59 - 0.99), although in age-stratified analyses, a significant relationship was present only in women age 70 or older. Receipt of guideline-concordant treatment was independently associated with lower overall mortality (HR = 0.65, 95% CI 0.54-0.80; $p < 0.001$). However, addition of the variable indicating receipt of guideline treatment did not substantially alter point estimates of hazard ratios for overall mortality for any given BMI category compared to the reference category, or for a 5 kg/m^2 difference in BMI. BMI was not associated with death from breast cancer. Guideline-concordant treatment was independently associated with lower breast cancer mortality (HR = 0.75, 95% CI 0.58-1.00; $p = 0.047$), although in stage-specific analyses the relationship between guideline treatment and breast cancer mortality was significant only among women with Stage III disease. In models of breast cancer mortality, there were no substantial differences in HR point estimates between models incorporating, and not incorporating, guideline treatment as a covariate.

Conclusion:

Contrary to our hypotheses, we found that breast cancer mortality was not higher among women with greater BMI, and that among older women, overall mortality was actually moderately lower among women whose BMI was higher. Although it appeared that women with higher BMI were slightly more likely to receive overall guideline-concordant treatment, receipt of guideline treatment did not mediate the relationship between BMI and mortality. Continuing research aimed at describing the extent to which multiple factors including treatment may explain

disparities in outcomes between obese and non-obese breast cancer patients can identify approaches to prevention and treatment that will have the most impact on breast cancer outcomes.

Introduction

Although advances in treatment have substantially reduced mortality after a diagnosis of locoregional breast cancer, persisting disparities in relative mortality related to patients' body size have been observed, with women who are obese having substantially poorer outcomes compared to non-obese patients. Further characterizing this disparity and addressing potential mechanisms behind it is an important public health goal.

Existing literature suggests that higher body mass (BMI) is associated with greater risk of death from any cause following a breast cancer diagnosis.[2-31] One recent meta-analysis showed that pre-diagnosis BMI was associated with substantially higher all-cause mortality after diagnosis (summary risk ratio = 1.41 for obese women versus those in the "normal" weight category).[10] Similarly, the existing body of evidence suggests that higher BMI is also related specifically to death from breast cancer; two recent meta-analyses showed pooled hazard ratios of 1.33 and 1.26 for breast cancer mortality for obese women compared to non-obese women.[30,31] It should be noted that while the majority of studies investigating these relationships found higher BMI to be associated with worse outcomes, some studies did not find this association,[12,34,37-43] or found it to be present only among certain sub-groups.[33,44,45] In the case of breast cancer-specific mortality in particular, some studies have reported that the association between BMI and poorer outcomes may not be present among younger women.[44,45] These findings suggest that studies of breast cancer survival according to BMI should consider a potential interaction with age or menopausal status.

Poor outcomes among obese patients likely reflect multiple factors. Obesity is associated with physiological risk factors for breast cancer mortality, including chronic inflammation and elevated levels of endocrine factors related to adipose tissue that are thought to promote tumor progression.[48,51,52] Obese patients may present with a more advanced stage due to delayed diagnosis, which can result from differences in screening patterns.[55,58,59] In addition to these factors, some evidence suggests that systematic differences in post-surgical treatment according to BMI may exist, with obese patients having a lower likelihood of receiving adequate treatment.[62,63,69,71-73,81] While little, if any, difference between obese and non-obese patients' treatment has been found to exist with regard to primary treatment,[79,80] some studies demonstrate that obese women may have been receiving inadequate doses of some hormonal therapies.[25,81] More notably, several studies have found frequently suboptimal adjuvant chemotherapy dosing among obese breast cancer patients,[62,63,69-73] despite evidence that delivering a dose based on actual, rather than "ideal" or "adjusted," body weight increases efficacy without higher incidence of toxicity-related adverse events.[62,69,74-77] Indeed, some studies have found that when chemotherapy is delivered at the appropriate dose intensity, patients with higher BMI have no worse prognosis compared to patients with lower BMI.[47,77] The body of evidence relating to adjuvant chemotherapy in obese patients has led to the inclusion of full body weight-based dosing in clinical guidelines.[78]

Studies formally investigating potential treatment-related mechanisms behind the relationship of BMI with mortality after breast cancer diagnosis are rare, particularly studies systematically comparing patients' treatment with standardized practice guidelines intended to improve these outcomes. To address in part the fact that little research has investigated the relation between

obesity and patterns of care as measured against widely disseminated clinical practice guidelines, we conducted analyses using data from a large, comprehensive study focused on patterns of care to examine whether disparities in treatment could be a mediating factor in the relationships between BMI and overall mortality or breast cancer mortality. In this study we compared overall and breast cancer mortality between women with higher and lower BMI in a study population of women all diagnosed in the same year with locoregional disease, but representing diverse geographic regions and demographic characteristics. We then examined, within the same population, variations in receipt of treatment that was in line with clinical practice guidelines specified by the National Comprehensive Cancer Network (NCCN), and aimed to determine how much, if any, of the association between BMI and overall or breast cancer-specific mortality might be partially explained by differences in receipt of guideline-concordant treatment.

Data and Methods

Data Sources

This study used data from the National Program of Cancer Registries (NPCR) Breast and Prostate Cancer Data Quality and Patterns of Care Study (POC-BP)[101] first to examine the relationship between patient body mass index (BMI) and mortality after a breast cancer diagnosis, and then to investigate the hypothesis that guideline-concordant treatment may be a mediator of this relationship. The POC-BP data set comprised breast and prostate cancer cases diagnosed in 2004 identified from population-based cancer registries in California, Georgia, Kentucky, Louisiana, Minnesota, North Carolina, and Wisconsin. Cases were selected for inclusion using stratified random sampling based primarily on racial and ethnic characteristics, but also including state-specific regional factors. Registry information was supplemented with

information abstracted by certified tumor registrars from medical records at hospitals and physicians' offices. Follow-up data on women's vital status were collected through the routine linkage of cancer registry data with death certificate data from state vital statistics departments as well as through NPCR-supported use of the National Death Index (NDI), which enabled identification of deaths occurring in states other than the one in which a patient was diagnosed.

Eligibility Criteria

Women 20 years or older diagnosed with primary breast cancer in 2004 (other than by autopsy or death certificate) were eligible for POC-BP if they had no previous diagnoses of *in situ* or invasive breast cancer, other reportable cancers, Paget's disease, Kaposi's sarcoma, or lymphoma. The focus of this analysis was locoregional invasive disease. A total of 6,967 patients with Stage I, II, or III disease were identified. Women who did not receive any surgery for their breast cancer (n = 105) were excluded from analyses. Women with certain cancer diagnoses not considered reportable by the tumor registries, including some skin carcinomas, carcinoma *in situ* of the cervix, borderline ovarian cancers, benign brain tumors, and lymphohematopoietic malignancies diagnosed before 2001 (n = 39), were excluded from the analytic data set. Women with unknown BMI (n = 1462), or for whom follow-up information on vital status was not available (n = 6), were also excluded. Finally, women were excluded if incompleteness in the information available regarding post-surgical therapies they received precluded determination of whether or not their post-surgical course of treatment was guideline concordant, as described below (n = 1135), leaving 4,220 women.

Outcomes

Time to death (all-cause, or overall, mortality) was defined as days between diagnosis and death from any cause. Time to death from breast cancer was defined as days between diagnosis and breast cancer-specific death, as determined from ICD-10 cause of death codes. Survival analyses included data on women's vital status through 8 years after the date of diagnosis.

Explanatory Variables

Body mass index (m/kg^2) was calculated based on weight and height information abstracted from physicians' records. Weight and height were measured at the time of diagnosis.

Receipt or nonreceipt of guideline-concordant treatment was investigated as a potential mediating variable in the relationship between BMI and the outcomes examined. Overall guideline-concordant postsurgical treatment was defined as treatment in concordance with the NCCN Clinical Practice Guidelines in Oncology version 1.2003,[103] the version applicable when these cases were diagnosed, for the post-surgical treatment domains of radiation therapy and adjuvant systemic therapies. The adjuvant systemic therapies examined were adjuvant chemotherapy, the specific adjuvant chemotherapy regimen a woman received, and hormonal therapy.

The guidelines for post-surgical radiation therapy make recommendations for receipt or nonreceipt (or optional receipt) of radiation according to the disease stage, type of surgery received, and characteristics of the tumor before surgery (see Fig. 1). Any patients for whom the guidelines recommended radiation therapy who did not receive this therapy, and any patients for whom the guidelines specified that radiation therapy should not be given who did receive this treatment, were considered to have received non-guideline-concordant treatment (under-treatment and over-treatment, respectively).

Adjuvant chemotherapy was recommended by guidelines depending on tumor characteristics (see Fig. 2). Patients who were 70 or older (N = 1161) and/or had certain rare histologic tumor types (N = 774) were not covered by the NCCN guidelines on adjuvant chemotherapy and were therefore considered to have received guideline treatment regardless of whether adjuvant chemotherapy was received. In addition, NCCN guidelines for systemic therapies recommend that physicians "consider adjuvant therapy" for patients with certain tumor characteristics, including mid-range size and/or colloid or tubular histology; since there was no single guideline-concordant treatment for patients with these tumor characteristics, they were also all considered to have received guideline care (N = 579).

Among patients who did receive guideline-concordant adjuvant chemotherapy, the specific regimen received was considered guideline-concordant if listed as an NCCN guideline-approved agent, or if received as part of a clinical trial.

Hormonal therapy, defined as orally administered tamoxifen or aromatase inhibitors (AIs), was recommended by the NCCN guidelines for all women with hormone receptor-positive (estrogen receptor (ER)- and/or progesterone receptor (PR)-positive) tumors.

If a woman's treatment was not concordant with the guidelines for one or more of the treatment domains examined, her treatment was considered not to be overall guideline-concordant; otherwise, she was categorized as having received guideline-concordant treatment.

Clinical and Demographic Covariates

Patient age was determined at time of diagnosis. Race/ethnicity information was obtained from patients' medical records, and from information found in Indian Health Services patient

registration. When Hispanic origin was unclear, a North American Association of Central Cancer Registries identification algorithm was used.[112]

Insurance status was categorized as private, Medicare or other public insurance only, Medicaid, uninsured, and unknown. The "private" category included patients with Medicare plus private supplemental insurance. Women who were dual-eligible for Medicare and Medicaid were grouped in the Medicaid category.

Education and socioeconomic status were based on census tract information for the patient's place of residence. Patients were categorized as living in a higher poverty (≥ 20% of residents below the federal poverty level) or lower poverty area, and as living in a lower education (≥ 25% of adults ≥ 25 years of age with less than high-school education) or higher education area. Residential areas were described as 100% urban, mixed, or 100% rural, using the 2000 U.S. Census Bureau's urban and rural criteria.

Tumor pathologic stage was categorized as I, II, or III based on American Joint Commission on Cancer (AJCC) staging criteria. Tumor grade was characterized by a I-IV score based on the degree to which cells were differentiated, with I being well-differentiated (more resemblance to normal breast tissue) and IV being undifferentiated; grade was also unknown in some cases. Hormone receptor status for estrogen receptors (ER) and progesterone receptors (PR) was classified as positive, negative, or unknown.

To characterize comorbidity burden present at the time of diagnosis, a modification of the Piccirillo (ACE-27) comorbidity index[105] was used; this considered each of 25 conditions (26 from the Piccirillo comorbidity index, minus obesity and not including the index breast cancer)

and assigned a 1-3 score for "level of decompensation," where 1 is Mild, 2 is Moderate, and 3 is Severe.

Statistical Analysis

First, overall mortality and breast cancer specific mortality were compared across BMI categories, as defined by the World Health Organization ("underweight" if BMI<18.5 kg/m^2, "normal" if BMI was 18.5-24.9 kg/m^2, "overweight" if BMI was 25.0-29.9 kg/m^2, "obese" if BMI was 30.0-34.9 kg/m^2, and "very obese" if BMI≥35 kg/m^2).[113] Hazard ratios (HR) and 95% confidence intervals for each outcome were estimated using Cox proportional hazards models with survey weights and stratification to account for the POC-BP sampling. Covariates were chosen *a priori* because of a known or potential relationship with BMI and with treatment choices, and included health insurance, education, socioeconomic status, urban/rural residence, tumor size, lymph node status, tumor grade, hormone receptor status, comorbidities, and tumor registry and patient race/ethnicity (the latter two by incorporating stratification according to the POC study's stratification variable, based on a design that stratified by registry and race). We calculated p-values for trend for each model by running a second version of the model in which BMI was represented by a continuous variable.

Next, a binary variable was added to each model (overall and breast cancer-specific mortality) indicating receipt or nonreceipt of overall guideline-concordant treatment, and the models were compared to assess whether a mediating effect was present by determining whether the addition of this variable significantly reduced the point estimate for the effect of BMI on the outcome being examined. Models for overall mortality with and without the guideline-concordance variable were produced specifically for women younger than age 70 and for age 70 or older, as

previous research indicated that the BMI-overall mortality relationship may differ between these age categories. Similarly, models for breast cancer mortality specific to each AJCC stage (I, II, and III) were produced because previous research indicated that the relationship between BMI and breast cancer mortality may differ according to tumor stage.

Results

Table 1 shows BMI according to demographic and clinical characteristics of the study population. Roughly one-third (36%) of the women included in the study population were obese (BMI > 30 kg/m^2), with 17% in the "very obese" category. Most of the remaining women were in the "overweight" category (30%) or the "normal weight" category (32%); less than 2% of women were underweight. Most women (71%) were between the ages of 40 and 69 at the time of diagnosis; a smaller proportion (22%) were 70 years of age or older, and even fewer (6%) were under age 40. Age and BMI were associated ($p < 0.001$); mean BMI was greater in higher age categories, except for among women ages 70-79 and women 80 years of age and older, the latter category of which had the lowest BMI. Age-adjusted analyses were conducted to examine associations between BMI and other demographic and clinical variables.

Most women (75%) were white. Race/ethnicity was associated with BMI ($p < 0.001$), with black women having the highest mean BMI (31.2 kg/m^2) and Asian or Pacific Islander women having the lowest (24.4 kg/m^2). The majority of women (63%) were privately insured. Insurance type and BMI were associated ($p < 0.001$); those insured by Medicaid had the highest average BMI, 30.0 kg/m^2, as compared to 28.1 kg/m^2 among those with private insurance. 82% of the women lived in low-poverty areas and 70% in high-education areas. Women in higher-education census tracts and in lower-poverty census tracts tended to have lower BMI ($p < 0.01$ for both).

Half of the women (54%) lived in urban areas. Women in rural areas tended to have higher BMI than women living in urban or mixed urban/rural areas, although the association was of borderline statistical significance ($p = 0.06$). Mean BMI also differed significantly according to the tumor registry through which a woman was identified ($p < 0.001$). The majority of women had Stage I (48%) or Stage II (35%) tumors at diagnosis. Higher AJCC stage was associated with higher BMI. The majority of cases (56%) had well- or moderately-differentiated tumors. Most patients (90%) had either no comorbid conditions or mild comorbidity. Greater BMI was found among women with comorbidity than among cases with no comorbidities ($p < 0.001$).

Five-year all-cause mortality was 14.8% (622 deaths by 5 years) and 5-year breast cancer-specific mortality was 8.5% (357 deaths due to breast cancer by 5 years). At eight years past the date of diagnosis, 19.7% of women were known to be deceased (832 deaths), with half of these deaths from breast cancer (437 deaths, 52.5%), and the remainder (all but 2 women) had been censored because vital status data were no longer being collected.

As an initial step in determining whether receipt of guideline-concordant therapy could be a mediating factor in the relationship between BMI and mortality after breast cancer diagnosis, we examined whether likelihood of receiving overall guideline-concordant treatment differed according to BMI. Table 2 presents odds ratios (OR) and 95% confidence intervals (CI) for receipt of overall guideline-concordant post-surgical therapy according to BMI category. Women in higher BMI categories had higher odds of receiving overall guideline-concordant treatment (OR for 5 kg/m^2 difference in BMI = 1.08, 95% CI 1.02 – 1.14; p-value for trend = 0.01).

Table 3 shows results of proportional hazards regression models investigating the relationship between BMI and all-cause or breast cancer-specific mortality and the potential

mediating influence of guideline-concordant treatment. Model I includes only BMI and the additional demographic and clinical covariates, while Model II incorporates the variable indicating receipt or nonreceipt of guideline-concordant treatment.

All-cause mortality

In Model I, not including the variable for guideline-concordant treatment, higher BMI appeared to be associated with lower hazard for overall mortality (HR for BMI of 30-34.9 kg/m^2 compared to BMI of 18.5-24.9 = 0.77, 95% CI, 0.59 - 0.99; p-value for trend = 0.04). In general, having 5 kg/m^2 higher BMI was associated with 7% lower hazard for overall mortality (HR = 0.93, 95% CI 0.87 to 1.00) in the group as a whole, although age-stratified analyses showed that the relationship between higher BMI and lower overall mortality hazard was significant only among women age 70 or older (Table 4, discussed later).

In Model 2, the variable for guideline-concordant treatment was added. Receipt of guideline-concordant treatment was independently associated with lower overall mortality (HR = 0.65, 95% CI 0.54-0.80; $p < 0.001$). However, the addition of the variable indicating receipt of guideline treatment did not alter the point estimates of the hazard ratios for overall mortality for any given BMI category compared to the reference category, or for a 5 kg/m^2 difference in BMI, by more than 0.01, with the exception of the HR for the lowest BMI category (BMI < 18.5 kg/m^2) compared to the reference category, which differed by 0.06 but still did not indicate a statistically significant difference in hazard between the lowest and reference categories.

Table 4 shows results of proportional hazards regression models for the BMI-overall mortality relationship stratified according to age category (under 70 years versus 70 years of age or older at diagnosis), with and without the proposed mediating variable (Model I and Model II,

respectively). Women were divided according to age into those 70 or older and those under age 70 due to earlier findings in women from the POC-BP study population which showed differences in the relationship between BMI and overall mortality between these two groups. In Model I, BMI was not found to be significantly related to all-cause mortality among women under age 70; among women age 70 or older, there was a suggestion that women in higher BMI categories, particularly women with BMI of 30-34.9 kg/m^2, had lower mortality compared to women in the reference category of 18.5 - 24.9 kg/m^2, although this relationship was of borderline statistical significance ($p = 0.06$). In Model II, BMI was still not significantly related to all-cause mortality among women under age 70, and among women age 70 or older, a borderline significant relationship was again observed ($p = 0.08$) in the same direction as for Model I. Among women under age 70, there was a suggestion that guideline-concordant treatment was associated with lower overall mortality, although the relationship was of borderline statistical significance (HR = 0.80, 95 % CI 0.62 - 1.04; $p = 0.09$). For women older than 70, receipt of guideline-concordant treatment was significantly associated with lower overall mortality (HR = 0.46, 95% CI 0.34 - 0.63; $p < 0.001$). However, addition of the guideline-concordance variable did not alter the hazard ratios for higher BMI categories compared to the reference category by more than 0.02.

Breast Cancer Mortality

In Table 3, hazards ratios for breast cancer mortality according to BMI category are presented for Model I (with the guideline-concordance variable) and Model II (without the guideline-concordance variable). BMI was not associated with breast cancer mortality in either of the models. Receipt of guideline-concordant treatment was independently associated with

lower breast cancer mortality (HR = 0.75, 95% CI 0.58 - 1.00; p = 0.05). Addition of the variable indicating guideline concordant treatment receipt to the first model did not alter the hazard ratios for any BMI category compared to the reference group by more than 0.02.

Table 5 shows results of proportional hazards regression models for the relationship between BMI and breast cancer-specific mortality according to AJCC stage, with (Model I) and without (Model II) the proposed mediating variable. Among women with Stage I disease, higher BMI was associated with higher breast cancer mortality (HR for BMI ≥ 35 kg/m^2 compared to BMI of 18.5 to 24.9 kg/m^2 = 5.09, 95% CI 1.94 - 13.35; p-value for trend = 0.004). Among women with Stage II or Stage III tumors, the relationship between BMI and breast cancer mortality was null (p-trend = 0.31 and 0.19, respectively). This was true in both Model I and Model II. Receipt of guideline-concordant treatment was found, in Model II, not to change the point estimates of hazard ratios for higher BMI categories compared to the reference group by more than 0.03. Among women with Stage I or Stage II disease, receipt of guideline-concordant treatment was not itself associated with breast cancer-specific mortality, but among women with Stage III disease, there was a significant association between guideline treatment and lower breast cancer mortality (HR = 0.67, p = 0.03).

Discussion

In this study, we used population-based tumor registry data to test multiple hypotheses, under the umbrella of an overarching conceptual framework in which we proposed that poorer outcomes among women with higher BMI after a breast cancer diagnosis might be partially explained by the mediating factor of lower likelihood of adequate treatment (with adequate treatment operationalized as receipt of therapies consistent with NCCN clinical oncology

guidelines). We hypothesized that BMI at diagnosis would be associated with higher overall mortality or breast cancer-specific mortality over the course of five to eight years of follow-up. Contrary to our expectations, in proportional hazards models adjusting for clinical and demographic characteristics, BMI was not associated with breast cancer mortality, and higher BMI was associated, albeit relatively modestly, with lower mortality from any cause among women age 70 or older at the time of diagnosis, with no relationship to all-cause mortality among younger women. The relationship between higher BMI and lower mortality among older women may be partially explained by a correlation between higher BMI and better functional status and overall health among older adults. The inverse relationship between BMI and mortality among older individuals has been documented among women and men in the general population, in a pattern referred to as an "obesity paradox" or "reverse epidemiology."[106] In line with this theory, while we attempted to adjust for comorbidities in our analyses, it is likely that we did not completely capture comorbidity burden, and that older women with lower BMI may have been more likely to have undiagnosed comorbid conditions or diseases not accounted for in the framework of the Piccirillo index.

We had also hypothesized that women in higher BMI categories would be less likely to receive post-surgical breast cancer treatment that adhered to clinical practice guidelines in the domains of radiation therapy and adjuvant systemic therapy, and that the lower likelihood of receiving guideline-concordant treatment might contribute to poorer outcomes among women with higher BMI. However, higher BMI at diagnosis was not associated with lower odds of receiving guideline-concordant therapy, and if anything seemed to predict greater likelihood of guideline therapy receipt.

Given these findings regarding BMI, mortality, and guideline-concordant therapy, it should be noted that the next step in our analyses, the investigation of guideline-concordant treatment as a mediating variable, took on a different character. With the associations between BMI and mortality indicating either a null relationship or a protective effect (for overall mortality among older women), and a moderate association between BMI and receipt of guideline-concordant treatment, we might now expect that if guideline treatment was a mediating variable, its addition into the models might increase, rather than decrease, the hazard ratio estimates for higher BMI categories. That is, rather than seeing lower odds of guideline treatment partially explaining a higher mortality hazard among women with higher BMI compared to the "normal"-weight reference group, the mediating effect of guideline treatment in this case might be to account in part for the null, or inverse, association between BMI and overall mortality.

Receipt of guideline-concordant treatment was associated with substantially lower mortality from breast cancer and even more strongly associated with lower mortality from any cause. This finding is in line with previous findings demonstrating substantial survival benefit from guideline-concordant cancer treatment.[84,90-94] Much of the existing literature on guideline concordant treatment and survival has focused on disease-specific mortality; we considered both breast cancer mortality and mortality from all causes. Notably, the relationship between guideline-concordant treatment and overall mortality was stronger than the relationship between guideline treatment and breast cancer mortality, and in stage-specific analyses guideline treatment was not significantly associated with breast cancer-specific mortality among women with early-stage disease. This finding raises a key issue with interpreting results regarding patterns of care and mortality. It suggests that the observed associations between guideline

concordance and improved outcomes may be due not (or not solely) to guideline adherence resulting in more effective treatment, but to guideline adherence being a proxy for better health and functional status (greater ability to withstand rigorous treatments and higher perceived ratio of benefit to risk). Previous studies, including an analysis by Kimmick et al reporting on women in the POC-BP data set, have demonstrated that patients with more comorbidities are more likely to be under-treated and less likely to receive guideline-recommended treatments.[83,92,120] In our analyses, as previously mentioned, comorbidity burden was among the covariates in multivariable models, but our means of accounting for comorbidities was not comprehensive; thus, it is likely that some residual confounding may have been present due to our inability to fully capture the health issues facing patients when treatment decisions were being made.

We did not find that accounting for receipt or non-receipt of guideline-concordant therapies, even among subgroups in which BMI and mortality were clearly related, made a difference in the significance or magnitude of the apparent relationship between BMI and mortality following a breast cancer diagnosis. This implies that differences in treatment, as measured by this specific metric, do not explain differences in mortality according to BMI.

Strengths and Limitations

In our analyses of overall and breast cancer mortality and receipt of guideline-concordant treatment, we made use of a large sample of patients all diagnosed in the same year with locoregional disease, but representing diverse geographic areas, racial/ethnic categories, and socioeconomic characteristics. Compared to many registry-based studies, the POC-BP data set was more complete due to the additional resources made available to the investigators to verify data and collect more detailed information on factors including comorbid conditions. Detailed

data were also available regarding women's post-surgical treatment. The study benefited from a relatively long follow-up period, with up to eight years' worth of data from most of the tumor registries represented, although given improved rates of breast cancer survival, even longer follow-up in such studies should be a priority. To our knowledge, no other study has evaluated whether clinical guideline-concordant treatment mediates the relationship between BMI and overall or breast cancer-specific mortality.

This study's findings should be considered in light of some important limitations. With over 4,000 women represented, the study population was large; however, it is possible that analyses may still have been underpowered. This is especially true of analyses involving subsamples, because due to generally good prognosis, particularly among women with early stage disease, the number of events (deaths, and in particular breast cancer deaths) was relatively small. Women with BMI < 18.5 kg/m2, considered "underweight," constituted a very small proportion of the study population, limiting our ability to examine outcomes among underweight women, who have in some other studies been found to have significantly higher mortality after a breast cancer diagnosis.[10] A larger sample size could potentially have allowed us to assess with greater confidence whether a U-shaped mortality curve according to BMI was present in our study population as well. Similarly, while the follow-up time was longer than in many studies, at five to eight years, additional follow-up data could have been helpful, especially in examining breast cancer mortality.

The generalizability of our findings is limited in the sense that although we did not find that guideline treatment mediated the BMI-mortality relationship, it was not possible to generalize from our results to determine whether treatment patterns could have explained poorer outcomes

among obese women in a study population (like those represented in much of the existing literature) where this pattern of poorer outcomes associated with obesity was more consistently observed. Changes in practice and in the NCCN guidelines since 2004 could also decrease the generalizability of the findings to current practice.

Defining high-quality breast cancer treatment is extremely challenging, given the complexity of treatments and the many choices involved, and even when employing the method of comparing treatment to a specific set of clinical guidelines, multiple approaches are possible. The way we defined overall guideline-concordant therapy differs from some other studies in that we treated women over 70 and women with rare tumor histologies as automatically having had guideline-concordant treatment in the domain of adjuvant chemotherapy. The number of women falling into one or both of these categories was substantial, and this classification strategy therefore likely had a not insignificant effect on the pattern of guideline-concordant treatment that we described. Although our characterization of guideline-concordant treatment was technically faithful to the guidelines, it adds a degree of challenge to the interpretation of findings regarding guideline treatment as a mediator of outcomes, particularly among older women. In addition, due to medical records that may not have been complete in listing conditions resulting in contraindication of some treatments, receipt of guideline-concordant treatment may have been slightly overestimated, although likely non-differentially. A significant limitation related to assessing treatment received was the fact that we were not able to assess chemotherapy dose intensity, which may be of greater concern with regard to mortality than receipt or nonreceipt of systemic therapy.

The very approach of using adherence to clinical guidelines as a means of capturing meaningful variations in the care that patients received also has benefits and limitations. Although guidelines serve an important purpose in decreasing inappropriate variations in care, and have been found in this study and others to be strongly related to lower overall and disease-specific mortality, given the importance of shared decision-making in patients' treatment, it would not actually be desirable to see universal adherence to guidelines, and indeed the NCCN guidelines were not designed with this in mind. Interpreting results regarding associations between guideline treatment receipt and mortality outcomes is challenging in light of the very real possibility that, at least in some women, guideline concordance in treatment may be a proxy for better overall health. Also, while the guidelines are intended to improve survival, they are also formulated with regard to balancing survival with quality of life; we were unable to assess this second, crucial outcome.

Other limitations relevant to the interpretation of these findings relate to measurement of the main predictor variable and covariates used. BMI is an imperfect measure of body shape and adiposity that may include systematically larger inaccuracies among older women,[110] and was used due to convention and to the lack of any superior measure in wide acceptance. Additional limitations include: lack of education and socioeconomic status measured at the individual level; low representation, despite oversampling, of some racial/ethnic subgroups; and the exclusion of 21% of otherwise eligible patients due to missing BMI data. Further discussion of missing height and weight data in this study population can be found in a Supplement (Appendix B).

Conclusion

This study examined potential disparities in patients' treatment experiences according to body mass index as a potential mediator between body size and mortality, addressing an incompletely understood aspect of the multifactorial pathway connecting obesity and poorer outcomes after a breast cancer diagnosis. It adds to the existing evidence by drawing on a population-based sample of breast cancer patients with locoregional disease all diagnosed in the same year, and by using a widely accepted set of clinical guidelines as a framework for describing treatment patients received in multiple therapeutic domains during first-course treatment. In contrast to our own hypotheses and the majority of findings regarding obesity and mortality after a breast cancer diagnosis, we found that breast cancer mortality was not higher among women with greater BMI, and that among older women in particular, overall mortality was actually moderately lower among women whose BMI was higher. Although it appeared that women with higher BMI were slightly more likely to receive overall guideline-concordant treatment, defined as treatment adhering to NCCN guidelines for radiation therapy and systemic therapy after surgery, receipt of guideline treatment was not found to mediate the relationship between BMI and mortality. Future studies on this subject should consider the possibility that BMI relates to outcomes differentially according to a woman's age at diagnosis, and should also emphasize methods with adequate sensitivity and specificity for characterizing women's comorbidity burden. Continuing research aimed at describing the extent to which multiple factors including treatment may explain disparities in outcomes between obese and non-obese breast cancer patients can identify approaches to prevention and treatment that will have the most impact on disease burden and mortality.

Figures and Tables

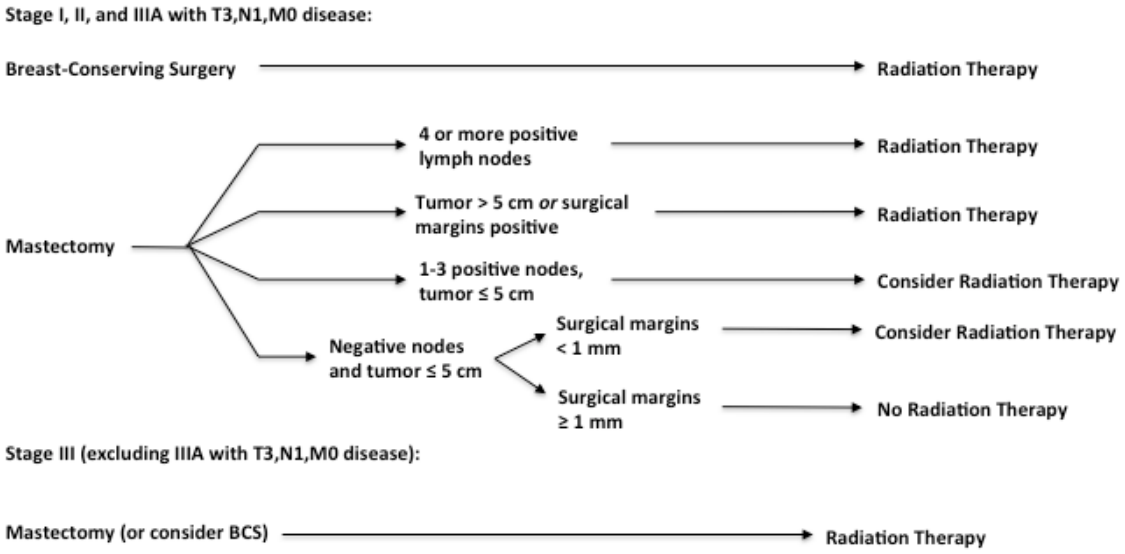

Figure 1. NCCN recommendations for radiation therapy after surgery.

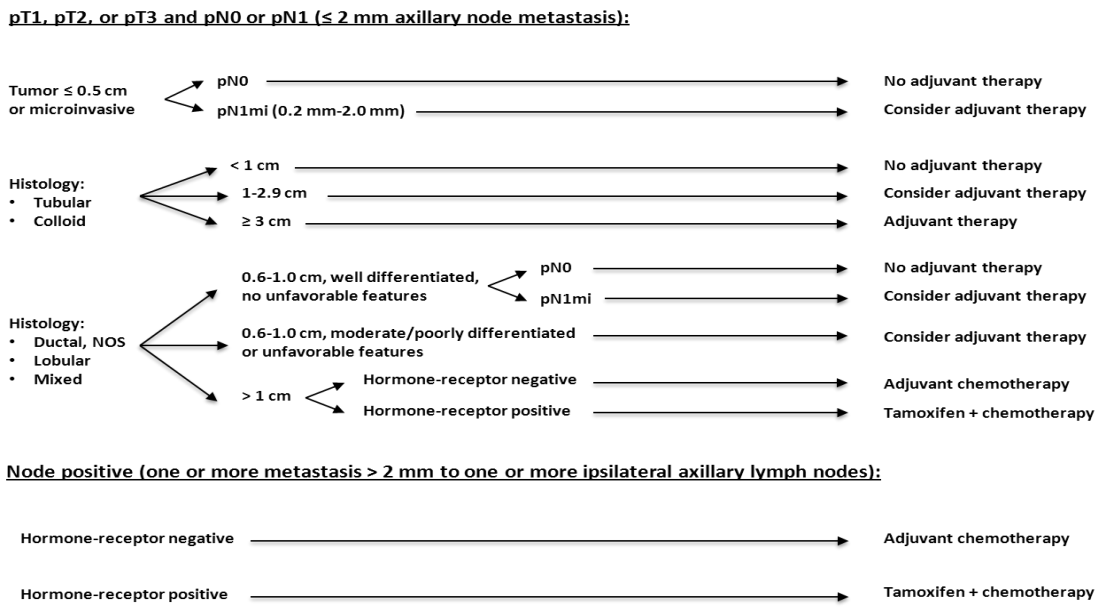

Figure 2. NCCN recommendations for adjuvant chemotherapy based on tumor characteristics in locoregional breast cancer

Table 1a. Breast Cancer Cases According to Body Mass Index and other Demographic and Clinical Characteristics
Stages I, II, and III Breast Cancer Patients from the POC-BP Study (2004)

Patient Characteristic	No.[1] (N = 4,220)	Weighted %	BMI (kg/m^2) Mean	SE	p-value[2]
BMI Category (kg/m^2)					
< 18.5	54	1.2			
18.5-24.9	1255	32.3			
25-29.9	1236	30.3			
30-34.9	877	19.4			
≥ 35	798	16.7			
Demographic Characteristics					
Age					
< 40	313	6.2	28.1	0.4	
40-49	989	22.1	28.6	0.2	
50-59	1150	27.6	29.4	0.2	< 0.001
60-69	905	22.0	29.4	0.2	
70-79	591	15.2	28.2	0.3	
≥ 80	272	6.9	26.7	0.4	
Race					
White, non-Hispanic	2341	74.7	28.0	0.1	
Black, non-Hispanic	1196	14.4	31.2	0.3	
AI/AN, non-Hispanic	31	0.2	29.8	2.1	< 0.001
API, non-Hispanic	245	3.4	24.4	0.5	
Hispanic	404	7.0	28.8	0.4	
Insurance					
Private	2548	63.4	28.1	0.2	
Medicare/other public	824	20.4	28.3	0.3	
Medicaid	597	10.5	30.0	0.3	< 0.001
None	131	2.0	28.3	0.7	
Unknown	120	3.7	29.0	0.5	
Census-tract education					
Higher	2584	69.8	28.0	0.1	< 0.001
Lower	1624	30.2	29.3	0.2	
Census-tract poverty					
Lower	3163	82.3	29.1	0.3	0.002
Higher	1045	17.7	28.2	0.1	
Urbanicity					
Urban	2195	53.5	28.1	0.2	
Urban/Rural mixed	1429	33.8	28.7	0.9	0.06
Rural	585	12.8	28.9	0.3	

(continued in Table 1b)

Abbreviations: AI/AN, American Indian/Alaska Native; API, Asian/Pacific Islander.
1. Totals may not add up to 4,220 due to missing values for some variables.
2. P-values from general linear models comparing means between categories adjusted for age.

Table 1b. Breast Cancer Cases According to Body Mass Index and other Demographic and Clinical Characteristics, continued

Stages I, II, and III Breast Cancer Patients from the POC-BP Study (2004)

Patient Characteristic	No.[1] (N = 4,220)	Weighted %	BMI (kg/m^2) Mean	SE	p-value[2]
Registry (State)					
1	469	16.7	28.5	0.3	
2	371	9.1	28.2	0.4	
3	458	11.6	28.6	0.3	
4	225	8.1	27.9	0.4	< 0.001
5	800	9.1	29.3	0.4	
6	992	18.2	28.9	0.3	
7	905	27.2	27.6	0.2	
Clinical Characteristics					
Tumor Stage (AJCC)					
I	1938	48.1	27.8	0.2	
II	1511	34.9	28.7	0.2	< 0.001
III	771	16.9	29.4	0.3	
Lymph Nodes					
Any positive	1546	34.4	29.1	0.2	
All negative	2474	60.8	28.2	0.2	< 0.001
Unknown[3]	200	4.8	27.1	0.5	
Tumor Size					
≤ 0.5 cm	308	7.9	27.7	0.4	
0.51 - 1 cm	662	16.3	27.4	0.3	
1.01 - 2 cm	1298	31.3	28.2	0.2	< 0.001
2.01 - 5 cm	1553	36.4	28.8	0.2	
> 5 cm	350	6.9	29.4	0.4	
Unknown	49	1.2	31.8	1.0	
Histologic Type					
Ductal	3153	74.1	28.4	0.1	
Lobular	267	6.5	29.1	0.4	0.01
Mixed ductal/lobular	260	7.2	27.1	0.4	
Other	540	12.2	28.5	0.3	
Grade					
Well differentiated	757	19.7	27.6	0.2	
Moderately differentiated	1593	38.5	28.5	0.2	
Poorly differentiated	1609	36.1	28.7	1.2	0.03
Undifferentiated	48	0.9	29.4	1.1	
Unknown/other	213	4.8	28.5	0.5	

Hormone Receptor Status[4]					
ER+ and/or PR+	3103	75.3	28.5	0.1	
ER- and PR-	1017	22.3	28.2	0.2	0.14
Unknown	100	2.5	27.1	0.7	
HER2 Receptor Status					
HER2+	1469	33.7	28.4	0.2	
HER2-	2147	51.7	28.3	0.2	0.88
Unknown	604	14.7	28.5	0.3	
Comorbidity					
None	1941	46.9	26.5	0.2	
Mild	1871	42.7	30.3	0.2	< 0.001
Moderate	285	7.4	29.0	0.4	
Severe	123	3.0	29.2	0.6	

Abbreviations: ER+, estrogen receptor-positive; ER-, estrogen receptor-negative; PR+, progesterone receptor-positive; PR-, progesterone receptor-negative; HER2+, human epidermal growth factor 2 receptor-positive; HER2-, human epidermal growth factor 2 receptor-negative.

1. Totals may not add up to 4,220 due to missing values for some variables.

2. P-values from general linear models comparing means between categories adjusted for age.

3. A separate model excluding women with missing information about lymph node status also showed that lymph node status was associated with BMI ($p = 0.001$).

4. Separate models examining ER status and PR status separately in relation to mean BMI showed that neither was significantly associated with BMI ($p = 0.15$ and $p = 0.11$, respectively).

Table 2. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Receipt of Guideline-Concordant Treatment Among Women With Stage I-III Breast Cancer, According to BMI Category

Treatment	Overall (N and %)	BMI					
		< 18.5	18.5-24.9	25 - 29.9	30 - 34.9	≥35	p-trend
Overall Guideline-Concordant Therapy							
Yes, N	1798 (42.6)	15	535	509	383	356	
No, N	2422 (57.4)	39	720	727	494	442	
Odds Ratio (95% CI)[1]		0.55 (0.29 - 1.04)	1 (ref)	0.87 (0.72 - 1.06)	1.12 (0.89 - 1.41)	1.15 (0.89 - 1.47)	
per 5 kg/m2 BMI Δ				**1.08** (1.02 - 1.14)			**0.01**

1. Model adjusted for age, tumor size, insurance type, poverty in census tract of residence, education levels in census tract of residence, urban/rural area, tumor grade, comorbidity level, and hormone receptor status. Survey sampling was stratified by tumor registry and by race/ethnicity.

Table 3. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for All-Cause Mortality and Breast Cancer-Specific Mortality According to Body Mass Index, Not Accounting (Model 1) and Accounting (Model 2) for Guideline-Concordant Treatment

	All-Cause Mortality			Breast Cancer-Specific Mortality		
	HR	95% CI	p-trend	HR	95% CI	p-trend
Model 1: Adjusting for Age, Tumor Stage, and Other Clinical and Demographic Characteristics[1]						
Body Mass Index (kg/m^2)						
< 18.5	1.18	0.63 - 2.23		0.35	0.11 - 1.12	
18.5-24.9	1 (ref)			1 (ref)		
25-29.9	0.84	0.66 - 1.07		0.88	0.62 - 1.24	
30-34.9	**0.77**	0.59 - 0.99		1.00	0.70 - 1.43	
≥35	0.87	0.66 - 1.14		0.90	0.61 - 1.35	
per 5 kg/m2 BMI Δ	**0.93**	0.87 - 1.00	**0.04**	0.97	0.89 - 1.06	0.54
Model 2: Adjusting for Age, Tumor Stage, and Other Characteristics, and for Receipt or Nonreceipt of Guideline-Concordant Treatment[2]						
Body Mass Index (kg/m^2)						
< 18.5	1.12	0.59 - 2.12		0.33	0.10 - 1.07	
18.5-24.9	1 (ref)			1 (ref)		
25-29.9	0.84	0.66 - 1.06		0.87	0.62 - 1.23	
30-34.9	**0.77**	0.59 - 0.99		0.99	0.69 - 1.42	
≥35	0.88	0.67 - 1.15		0.91	0.61 - 1.36	
per 5 kg/m^2 Δ	0.94	0.87 - 1.00	0.06	0.98	0.89 - 1.07	0.58
Guideline-Concordant Treatment Received	**0.65**	0.54 - 0.80	**< 0.001**	**0.75**	0.58 - 1.00	**0.047**

1. Model 1 adjusted for age, tumor stage, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status (estrogen receptor and progesterone receptor), and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity.

2. Model 2 adjusted for the same variables as Model 1, with the addition of a variable indicating receipt of guideline-concordant treatment. Guideline-concordant treatment was defined as treatment following National Comprehensive Cancer Network (NCCN) recommendations for radiation therapy, adjuvant chemotherapy, adjuvant chemotherapy regimen, and hormonal therapy.

Table 4. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for All-Cause Mortality According to Body Mass Index, Not Accounting (Model 1) and Accounting (Model 2) for Guideline-Concordant Treatment, Stratified by Age Category

	Under Age 70 (n = 3352)			**Age 70 or Older (n = 856)**		
	All-Cause Mortality			All-Cause Mortality		
	HR	95% CI	p-value	HR	95% CI	p-value
Model 1: Adjusting for Age, AJCC Stage, and Other Clinical and Demographic Characteristics[1]						
Body Mass Index (kg/m^2)						
< 18.5	0.93	0.36 - 2.39		1.70	0.74 - 3.94	
18.5-24.9	1 (ref)			1 (ref)		
25-29.9	0.93	0.68 - 1.28		0.79	0.56 - 1.12	
30-34.9	0.85	0.61 - 1.19		0.70	0.46 - 1.07	
≥35	0.89	0.62 - 1.27		0.91	0.58 - 1.44	
per 5 kg/m^2 BMI Δ	0.96	0.89 - 1.04	0.28	0.87	0.76 - 1.00	0.06
Model 2: Adjusting for Age, AJCC Stage, and Other Characteristics, and for Receipt or Nonreceipt of Guideline-Concordant Treatment[2]						
Body Mass Index (kg/m^2)						
< 18.5	0.90	0.35 - 2.31		1.50	0.59 - 3.84	
18.5-24.9	1 (ref)			1 (ref)		
25-29.9	0.92	0.67 - 1.27		0.77	0.55 - 1.09	
30-34.9	0.86	0.61 - 1.20		0.71	0.47 - 1.07	
≥35	0.89	0.63 - 1.27		0.93	0.58 - 1.50	
per 5 kg/m^2 BMI Δ	0.96	0.89 - 1.04	0.32	0.89	0.77 - 1.01	0.08
Guideline-Concordant Treatment Received	0.80	0.62 - 1.04	0.09	**0.46**	0.34 - 0.63	< 0.001

1. Model 1 adjusted for AJCC Stage, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status (estrogen receptor and progesterone receptor), and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity.

2. Model 2 adjusted for the same variables as Model 1, with the addition of a variable indicating receipt of guideline-concordant treatment. Guideline-concordant treatment was defined as treatment following National Comprehensive Cancer Network (NCCN) recommendations for radiation therapy, adjuvant chemotherapy, adjuvant chemotherapy regimen, and hormonal therapy.

Table 5. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Breast Cancer Mortality According to Body Mass Index, Not Accounting (Model 1) and Accounting (Model 2) for Guideline-Concordant Treatment, Stratified by Tumor Stage

	Stage I			**Stage II**			**Stage III**		
	Breast Cancer Mortality			Breast Cancer Mortality			Breast Cancer Mortality		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Model 1: Adjusting for Age, Tumor Stage, and Other Clinical and Demographic Characteristics[1]									
Body Mass Index (kg/m^2)									
< 18.5	2.47	0.51 - 14.71		not estimable			0.31	0.05 - 1.81	
18.5-24.9	1 (ref)			1 (ref)			1 (ref)		
25-29.9	1.29	0.55 - 2.99		0.94	0.48 - 1.87		0.72	0.45 - 1.15	
30-34.9	1.04	0.42 - 2.55		0.88	0.45 - 1.71		0.98	0.61 - 1.57	
≥35	**5.09**	1.94 - 13.35		0.84	0.40 - 1.77		0.65	0.38 - 1.11	
per 5 kg/m2 BMI Δ	**1.45**	1.13 - 1.87	**0.004**	0.91	0.76 - 1.09	0.31	0.93	0.83 - 1.04	0.19
Model 2: Adjusting for Age, Tumor Stage, and Other Characteristics, and for Receipt or Nonreceipt of Guideline-Concordant Treatment[2]									
Body Mass Index (kg/m^2)									
< 18.5	2.75	0.51 - 14.95		not estimable			0.28	0.05 - 1.64	
18.5-24.9	1 (ref)			1 (ref)			1 (ref)		
25-29.9	1.29	0.55 - 3.00		0.94	0.48 - 1.87		0.72	0.45 - 1.14	
30-34.9	1.04	0.42 - 2.56		0.89	0.46 - 1.47		0.95	0.59 - 1.54	
≥35	**5.09**	1.96 - 13.22		0.85	0.40 - 1.79		0.66	0.38 - 1.12	
per 5 kg/m2 BMI Δ	**1.45**	1.12 - 1.87	**0.004**	0.91	0.76 - 1.10	0.34	0.93	0.83 - 1.04	0.20
Guideline-Concordant Treatment Received	1.10	0.55 - 2.20	0.78	0.81	0.49 - 1.32	0.39	**0.67**	0.46 - 0.97	**0.03**

1. Model 1 adjusted for age, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status (estrogen receptor and progesterone receptor), and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity.

2. Model 2 adjusted for the same variables as Model 1, with the addition of a variable indicating receipt of guideline-concordant treatment. Guideline-concordant treatment was defined as treatment following National Comprehensive Cancer Network (NCCN) recommendations for radiation therapy, adjuvant chemotherapy, adjuvant chemotherapy regimen, and hormonal therapy.

CHAPTER SEVEN: DISCUSSION AND CONCLUSIONS

In this study, we used data from a large, tumor registry-based study representing women from seven different states to address research aims related to the previously observed pattern of poorer outcomes among obese breast cancer patients. We hypothesized that women with higher BMI would experience, on average, higher overall mortality and breast cancer-specific mortality and have a lower likelihood of receiving treatment that followed National Comprehensive Cancer Network guidelines; and that this lower likelihood of guideline-concordant treatment might be found to contribute to the poorer mortality outcomes. If our results had indicated this was the case, it would have suggested that differential treatment might be a key component of the multifactorial relationship connecting obesity and mortality after a breast cancer diagnosis, and one that – unlike some of the biological pathways that have been investigated – could be addressed by changes on the level of the provider or health care practice. However, our findings on both mortality and guideline concordant treatment according to BMI were in contrast with our expectations.

Results showed that women with higher BMI did not have an increased hazard for death from breast cancer, with the exception of women who had Stage I disease, among whom breast cancer mortality was substantially higher among women in the highest range of BMI (35 kg/m^2 or greater). Furthermore, higher BMI was not associated with higher overall mortality as we had predicted, and older women with higher BMI were found to experience lower all-cause mortality. Among women over 70, overall mortality was lowest among women in the top two BMI categories and significantly higher among underweight women, with an overall trend indicating a significant protective effect of higher BMI among women in this age category. One potential reason for this correlation is an incomplete adjustment for comorbidity burden. The

Piccirillo index, although advantageous with regard to representing number and severity of conditions, is not comprehensive, and medical records from which data were abstracted to create the comorbidity index values were not necessarily complete. Thus, it is possible women who were older and had lower BMI were more likely to have undiagnosed comorbid conditions, conditions not recorded in the medical record, or diseases not accounted for in the Piccirillo index's format. The association could also be explained by a correlation between higher BMI and better functional status among older adults. The null relationship between BMI and overall mortality among women under 70 was nonetheless surprising, and notable in that it is contrary to findings in much of the existing literature. It is possible that there was a lack of sufficient statistical power to detect a difference in mortality according to BMI among these women; however, the sample size was comparable, if not larger, to that used in several studies that did report such a relationship, and the hazard ratio point estimates were close to 1.

Our findings on obesity and receipt of guideline-concordant treatment also indicated either no association (within specific therapeutic domains) or an association in the opposite direction from that expected. Women with higher BMI were moderately more likely to receive overall guideline-concordant treatment, defined as treatment adherent to clinical guidelines for radiation therapy, adjuvant chemotherapy (including a guideline-approved regimen), and hormonal therapy. Fewer than half of all women received treatment that was overall guideline-concordant. Although for the most part women with higher BMI in general appeared to be more likely to receive guideline-concordant treatments, among women with Stage I disease, an association was found between higher BMI and lower likelihood of receiving guideline-concordant treatment in the domain of adjuvant chemotherapy. This is notable in light of the fact that women with Stage I disease were also the only subgroup examined in which a positive association between higher

BMI and breast cancer mortality was observed. With information only on appropriate initiation of adjuvant chemotherapy, it is hard to speculate with confidence that higher BMI contributed to worse outcomes in this group, but this finding strongly suggests that additional research addressing this question should be conducted, using more detailed medical information (for example, chemotherapy dose or rates of chemotherapy course completion), among women with Stage I disease.

Findings regarding guideline-concordant chemotherapy and overall guideline-concordant treatment were for the most part borne out in sensitivity analyses in which alternate versions of the definition for chemotherapy were used (see Appendix D, Tables D4 and D5). These alternate definitions entailed using different approaches to classify women who were over 70 or who had tumors with rare histology types, who were treated in the main analyses as automatically having received guideline-concordant chemotherapy, since they are not covered by the 2003 guidelines.

Even though we did not see the expected results in our Aim 1 or Aim 2 analyses, we continued on to test the mediation hypothesis, following the logic that (as described in Chapter 6), it was possible that a higher likelihood of guideline-concordant treatment could be an intermediate step in the observed association between higher BMI and equivalent or lower mortality. However, although receipt of guideline-concordant treatment was independently associated with better outcomes, adding a variable to account for guideline-concordant treatment receipt to models for overall or breast cancer mortality made very little difference in the significance or magnitude of the apparent relationship (or lack of relationship) between BMI and mortality following a breast cancer diagnosis, implying that differences in treatment, as measured by the specific metric used in this study, do not explain differences in mortality according to BMI.

Strengths and Limitations

This study took the approach, very infrequently used previously, of emphasizing the comparison of patients' treatment experiences according to body size with reference to clinical oncology guidelines in the attempt to address, in part, an incompletely understood aspect of the multifactorial pathway connecting obesity and the tendency for poorer outcomes after a breast cancer diagnosis. It adds to the evidence from earlier studies on differences in mortality according to BMI, as well as differences in patterns of care related to obesity, by drawing on a large, stratified random sample of patients all diagnosed in the same year with locoregional disease but representing diverse geographic areas and racial, ethnic, and socioeconomic categories. The POC-BP data set also contains more complete data than many registry-based studies, as tumor registries do not have the resources made available to the POC-BP investigators to verify data and obtain detailed information on treatment patients received at non-hospital settings. This study used a well-known, widely accepted set of clinical guidelines as a framework for describing potential differences in the surgical procedures, radiation, and adjuvant therapies that patients received during first-course breast cancer treatment.

The POC-BP data set used for this study includes some limitations that are important to consider in interpreting the results. One notable limitation is the fact that information on dose or dose density of adjuvant chemotherapy is not available through this data set and therefore we were unable to determine whether or to what extent reduced dose intensity was an issue among the group of patients studied. In addition, because no data on breast cancer recurrence were available, we were unable to determine whether the relationship between obesity and recurrence in this study population replicated that found elsewhere. We were also not able to assess whether

differences in the relationships between obesity and mortality, or obesity and receipt of guideline treatment, differed according to whether or not women had gone through menopause, as a number of previous studies have suggested; instead, we were restricted to investigating potential interactions according to age, which, while clearly related to menopause, is a different construct with differing implications. Use of an age cutoff as a proxy for menopause was considered but rejected, due in part to the fact that a substantial proportion of women in the study may have undergone an oophorectomy to reduce recurrence risk, decoupling age from menopausal status.

The use of BMI as the main predictor variable is also a limitation of the study. Like the great majority of studies relating body size or adiposity to cancer outcomes, this study used BMI as the sole means of measuring these characteristics. Since we were conducting a retrospective analysis using an existing data set, we did not have the option of using alternate measures of body fatness, such as waist-to-hip ratio or body fat as measured by the caliper skinfold method, not to mention more intricate methods, as some researchers have proposed and used, such as magnetic resonance imaging (MRI), ultrasound, and dual-energy X-ray absorptiometry.[110,111,121] In one sense, the use of BMI was a benefit, in that our study's findings are in this regard comparable to the majority of existing research. However, the BMI categories we used in logistic regression models (as defined by the World Health Organization), while almost universally used in modern research related to obesity, are based on cutoffs that can reasonably be described as arbitrary from a biological perspective – one author has described the accepted categories as delineating obesity as a condition "based on relatively robust statistical, rather than direct physiological criteria"[121] – and furthermore, BMI is itself problematic as a measure of body habitus.

Limitations of BMI as a proxy for adiposity include its unreliability among individuals at the low and high ends of the height spectrum and (particularly relevant to this study) the fact that it appears to be systematically worse, as a means of characterizing adiposity and body shape, as individuals age.[110] In addition, it is not a precise or consistent measure of body composition,[110,111,121] in that it does not capture the differential contributions of muscle and adipose tissues to a person's body weight; individuals with the same BMI may have very different body compositions in terms of fat and lean tissue.[121] (For example, individuals whose BMI is "normal," but who in fact have an abnormal metabolic profile or are in poorer physical condition, may be erroneously assumed to be at lower risk for poor outcomes.[111]) This limitation has been recognized in the breast cancer literature, for example, by Vitolins et al, who concluded there was a high likelihood that more so than BMI, "tissue quality" was an important predictor of breast cancer recurrence, with women who had more adipose tissue at higher recurrence risk than women with equal weight but more lean tissue.[28] In addition to failing to accurately gauge a patient's percent body fat, BMI does not account for the distribution of adipose tissue within the body, a key limitation in light of the strong evidence suggesting that body fat distribution – the proportion of fat tissue concentrated viscerally as opposed to subcutaneously, and/or the proportion located in the central abdomen as opposed to peripherally in the lower body – is strongly associated with disease risk and breast cancer outcomes.[111,121,122] One recent study highlighting this limitation used MRI to examine body fat distribution. The study found that patients with a given BMI vary widely in body fat content and distribution; for example, among women with a BMI of 24 kg/m^2, percent body fat was found to vary from 30% to 44%.[111] There appears to be a trend in more recent studies of obesity-related outcomes toward collecting data on waist-to-hip ratio as a non-invasive and non-costly corollary to data on BMI that at least gets

closer to capturing an individual's distribution of adipose tissue, but as of yet, the number of studies using this method in breast cancer research is small.[33]

While alternate measures of adiposity were unavailable, some of our sensitivity analyses did explore alternative strategies to the approach of model-building using BMI and standardized BMI categories. The first of these was to carry out the same analyses used in Aim 1 (examining overall and breast cancer mortality) with body weight rather than BMI as the main predictor variable. In sensitivity analyses focused on body weight as an alternative to BMI, we first calculated hazards ratios for overall mortality and breast cancer-specific mortality in the in the set of women used for the analytic data set in our Aim 1 analyses (Table C1 in Appendix C), and then ran the same models using the slightly analytic data set comprising all women with known body weight (Table C2 in Appendix C). The latter set of analyses was also intended to partially address the issue of missing BMI, as it reduced the number of women not included due to missing data. Results from both sets of analyses using body weight in place of BMI closely mirrored the results from the BMI-based Aim 1 models reported in Chapter 4.

We also recognized that the standard BMI category cutoffs, while useful in comparing results between studies, may not accurately reflect the true points of inflection, so to speak, of the BMI-risk curve. To explore the possibility of other cutpoints that would more closely reflect differences in the outcomes of interest, we conducted recursive-partitioning analyses using continuous BMI and the variables included in our main analyses. In the recursive partitioning approach, data are split into homogeneous groups (groups with the most similar in terms of likelihood of experiencing the outcome of interest) on the basis of continuous or categorical explanatory variables; this occurs in an iterative process, with each split based on a rule based on a single explanatory variable. The end result is a tree with "branches" showing the splits that

occurred in the calculation process. Results from these sensitivity analyses are reported in Appendix C (Aim 1 models) and Appendix D (Aim 2 models). Briefly, BMI did appear to be an important predictor of overall mortality in recursive partitioning models, although not for all women, and the values at which splits occurred were not always the same as the standard BMI cut points (for example, in each of two different trees, 28 kg/m^2 and 38 kg/m^2 emerged as meaningful cutpoints; see Figure C2a and Figure C2c). BMI did not emerge as an important predictor of breast cancer mortality among all women, but among women with Stage I disease specifically, regression tree splits did occur according to BMI among women with higher-grade, PR+ disease and among women with PR- disease who were under age 80. A classification tree constructed in sensitivity analyses for Aim 2 did not show that overall guideline-concordant treatment was an important predictor of guideline treatment (instead, tumor registry, tumor size, node status, and age were the variables on which splits were based); however, results from the random forests procedure, which averages the result of a large number of hypothetical trees, did show that BMI was important in modeling overall guideline treatment.

As a descriptive means of exploring the true shape of the BMI-mortality curve, we also created models based on cubic splines and graphed the resulting hazards ratios; these graphs are shown in Appendix C. Models for overall mortality reflected, for the most part, a moderately decreased mortality hazard among women with higher BMI, although a strong linear relationship was not apparent in women with BMI greater than 22 kg/m^2 (the reference BMI). More striking, both in all women and the subset aged 70 or older, was the strong association between lower BMI (less than 22 kg/m^2) and higher overall mortality hazard. The model for breast cancer mortality according to BMI among all women showed an essentially flat curve, in line with our findings in Aim 1 that BMI and breast cancer mortality were unrelated for the group of women

as a whole. The model for breast cancer mortality according to BMI among women with Stage I disease, however, showed a curve roughly flat in the 14 kg/m^2 to 30 kg/m^2 range, but then inclining sharply upward before leveling off. This curve, indicating hazards ratio estimates greater than 5.0 for women in the upper BMI range (43 kg/m^2 or greater), reflected the same pattern observed in our findings from Aim 1 analyses, although the spline-based model provides a more detailed approximation of the apparent shape of the relationship.

Other limitations in the measurement of independent variables include the fact that education and socioeconomic status were measured at the census-tract level, rather than at the level of the individual. Data on patients' insurance type could be said to partially reflect SES, as it is sometimes used as a proxy for SES or income, but it is not a perfect one, particularly among older patients.

Missing data on height and/or weight pose a potential threat to the validity of the findings from our models using only women with known weight and height. 21.3% of the women in the parent data set who were otherwise eligible to be included in analytic data sets were excluded due to missing data on weight (0.9%), height (8.7%), or both (11.8%), and it seemed likely that these data were not missing completely at random. Age-adjusted linear regression models were used to compare the proportion of patients with missing height or weight across the explanatory variables used in our regression models. Results from these analyses showed that several demographic and clinical variables were associated with likelihood of missing weight and/or height data (Appendix B). The level to which this should be concerning is difficult to determine, in particular with regard to results relating to mortality. While we observed patterns of higher likelihood of missing BMI according to variables considered particularly relevant in predicting mortality, these patterns were inconsistent with regard to the association between missing BMI

and favorable or unfavorable prognostic characteristics. Women who were older were more likely to have missing BMI, but a greater probability of missing BMI information was also found among women with a lower tumor stage or a greater comorbidity burden at the time of diagnosis. The relationship between missing BMI and variables especially relevant to the likelihood of receiving guideline-concordant treatment was more straightforward. Women with missing BMI were more likely also to have some characteristics that, in our models, were independently associated with lower likelihood of guideline treatment receipt, suggesting that our estimates of the proportion of women receiving guideline-concordant treatment may have been artificially high. A pattern was also observed in which women with missing BMI were also more likely to have unknown values for some other variables, suggesting that women excluded due to missing BMI may have been more likely to have less complete medical records. In addition, it is possible that they were less likely to have recommended testing (for example, of tumor estrogen receptor status). This could potentially be an issue if, for example, medical record completeness reflected facility characteristics associated with poorer outcomes. Assessment of outcome trends related to facility-level variables was not within the scope of this analysis (although models for Aim 2 analyses did account for clustering by facility).

Given the high frequency of missing data on height and/or weight, we took additional steps to address the issue of potential bias resulting from these missing data. In addition to the sensitivity analyses using body weight instead of BMI described earlier, we employed a multiple imputation approach to estimate BMI among women with missing data on weight and/or height. Table C3 in Appendix C presents a comparison of results from regression models for mortality using the data set including some women with BMI based on imputed values to those including women with known BMI only. The results from models focusing on overall mortality (Table

C3a) were similar to the findings reported in Chapter 4, with lower hazard for mortality associated with higher BMI categories, although hazards ratios were for the most part closer to 1 (null findings), and the association between BMI and mortality was no longer statistically significant ($p = 0.13$). Results from models focusing on breast cancer mortality (C3b), like those reported in Chapter 4, also showed no association between BMI and disease-specific mortality among the group as a whole.

Some concerns about the generalizability of our results are relevant as well. Despite the study design's attempt to oversample racial and ethnic minorities and underrepresented geographical areas, the demographic characteristics of the group may not have been entirely representative of the population of U.S. breast cancer patients. One notable area of potential concern is that the great majority of the women in the POC-BP study lived in higher-income, higher-education areas; however, this may actually be true of breast cancer patients as a whole (as compared to other patient groups). [123,124]

Another potential generalizability concern stems from the fact that changes in the NCCN guidelines since 2003 could mean findings regarding guideline concordance would not be replicable if we were to examine a data set of women diagnosed more recently. We did conduct a sensitivity analysis for the third study Aim, investigating whether our findings would be different if the 2014 NCCN guidelines were used to define women's treatment as guideline-concordant or non-concordant. This is naturally an academic exercise, since the evidence base informing the 2014 guidelines may not have existed in 2003, or been strong enough to be codified into guidelines. However, conceptually it is important to consider, when asking if guideline-concordant treatment acts as a mediator between obesity and mortality after a breast cancer diagnosis, whether receipt of treatments now considered to be optimal on the basis of current

evidence actually predicted better survival, and whether this might explain some differences in mortality outcomes according to BMI. Results of this sensitivity analysis are reported and discussed in Appendix E. Briefly, they were for the most part similar to the findings resulting from our Aim 3 analyses (reported in Chapter 6), with a few exceptions. The proportion of women considered to have received guideline-concordant treatment was substantially lower when using the 2014 guidelines as a reference (24% as compared to 42%); this was driven in large part but not entirely by the fact that the 2014 guidelines recommend trastuzumab as an accompaniment to all adjuvant chemotherapy, and this treatment was prescribed very rarely in 2004-2006, when women in the study population would have been receiving their chemotherapy. Guideline-concordant treatment was, as found in analyses for Aim 3, independently associated with lower overall mortality, but was not significantly associated with lower breast cancer mortality (in contrast with findings from Aim 3 analyses). As found with the guideline-concordance variable based on 2003 guidelines, the addition of a variable indicating receipt of treatment in line with the 2014 guidelines had very little effect on the point estimates of hazard ratios for overall mortality or breast cancer mortality.

Beyond the question of whether findings based on 2003 guidelines are generalizable, it should also be noted that the very use of clinical practice guidelines, even widely recognized and respected recommendations such as the NCCN guidelines, has some limitations as a way of gauging appropriateness or quality of cancer treatment. Although we explicitly do not interpret our results as reflecting differences in quality of care, the assumption behind the use of clinical guidelines is that they promote more optimal clinical decision-making and increase quality of care, and indeed guidelines are increasingly being put to use as a basis for quality measures.[84,88] The NCCN guidelines provide clear recommendations, in the form of decision pathways and

lists, based on patient and disease characteristics; but these almost exclusively take the form of a yes or a no, with some "consider"s, on various types of treatments. Footnotes allow for some modification and nuance (for example, a footnote to a chemotherapy recommendation provides guidance in cases of older women with good prognosis by pointing out that among these women in particular, the incremental benefit of chemotherapy may be small), but overall, the guidelines are – purposefully—detailed yet simple. Our coding of women's treatment as guideline-concordant or non-concordant in the domains examined was, out of necessity related to the data available, even more simplistic; we did not account for features of treatment such as dose of radiation or whether a radiation boost was given, or length of time for which hormonal therapy was prescribed, but instead focused on creating binary variables reflecting whether or not treatment was initiated within a given domain as recommended by guidelines. Thus, the level of granularity in our assessment was a limitation.

Some more fundamental considerations regarding the use of guidelines as a process measure in general should also be mentioned. Clinical guidelines have the potential to convey substantial benefit in general and specialty care settings by reducing variation and improving the consistency of care, and up-to-date guidelines based on the highest levels of evidence can be a powerful resource for clinicians. However, the number of different guideline sets available to physicians in most specialties is large and increasing over time, and these sets of guidelines are frequently not consistent with each other,[88,125] leading to information overload and frustration. Given this, it may be unrealistic to conclude that physicians who did not follow one particular guideline set were not "adhering to guidelines." Even aside from the matter of multiple differing guideline sets, perfect adherence to guidelines is not desirable, as treatment must be tailored to fit the individual patient's needs and preferences, leaving the researcher in the difficult position of

trying to interpret low adherence rates (essentially, the question is "how low is too low?"). Interpreting results regarding guideline treatment is also complicated by the possibility that guideline-concordant treatment is a proxy for overall health in cancer patients. Despite these issues, from a research perspective, comparing treatments received to a single guideline set still provides a useful standard for determining whether those patterns of care differed according to other variables of interest. Some other issues that have been raised with regard to clinical guidelines include concerns related to their trustworthiness and potential unintended negative consequences. Some guidelines may be based less on evidence and more on expert opinion or consensus.[125] Experts developing guidelines may, through human error, include incomplete or incorrect evidence, or may fail to correctly interpret or synthesize the evidence available.[125,126] Guideline development may even, in some cases, be affected by ulterior motives, as specialists may write, or push for the shaping of, guidelines emphasizing their role in the care process, thus potentially contributing to overtreatment; there is some concern, too, that politics and industry may not be entirely divorced from the development process in some cases.[125] These limitations, and potential limitations, of clinical guidelines in general constitute an important caveat to any research findings using guideline concordance as a measure of care received. They may, however, be mitigated by the use of a guideline set such as the NCCN guidelines, which explicitly delineate the evidence base and process used to determine recommendations and identify not only evidence sources but the strength of the evidence behind each recommendation using a category-based system. The NCCN guidelines are also developed by a diverse group of clinicians, researchers, and patient advocates.

Finally and perhaps most critically, when interpreting findings like the results in our Aim 3 analyses shown in Chapter 6, it must be considered that although the NCCN clinical guidelines

are intended to improve survival outcomes, they are also meant to factor in impacts on quality of life. This tradeoff is challenging to capture numerically, and beyond the scope of this project, but it is a critical point to consider in any research related to guidelines and mortality.

Future Directions

A number of questions were outside the scope of this study that, nonetheless, would be very valuable to address in future studies in this area. These are discussed briefly below.

Longer-term survival and recurrence

Given the high proportion of women who live well beyond five to eight years past a breast cancer diagnosis, longer-term follow-up will be critical in gaining a full understanding of the relationships between obesity, treatment, and mortality that we investigated in this study. The POC-BP study is no longer funded, and thus all reporting of vital statistics is being supported by the individual tumor registries; this will allow for some additional data, but the follow-up information will not be as geographically representative as the first five years' worth of data. In this study, since collection of data on women's vital status fell off starting at 5 years after diagnosis, a large proportion of women in the study had been censored before 7 years, a point at which a "bump" in recurrence has been found to occur; thus, we had little statistical power to assess differences in survival past this clinically important point. Future studies designed along similar lines would ideally support collection and reporting of data on women's vital status and causes of death for a longer period of time. Similarly, while the POC-BP study data included information on time to death and cause to death, information on recurrence rates was not available. While in a sense recurrence is a secondary outcome, since it is so closely related to mortality, measuring recurrence separately could be important given its separate impact on quality of life, financial implications for patients, and costs within the health care system.

Breadth and depth in examination of treatment domains

While this study investigated the experiences of obese patients compared to non-obese patients in multiple domains of breast cancer treatment, treatment for this disease is complex and evolving, leaving additional treatment domains to be explored. Neoadjuvant therapies and surgical decision-making, which are both important components of the treatment process that also contribute to the decision-making pathways further down the line, could be investigated to determine whether treatment disparities according to patients' body size or adiposity exist.

In addition, as hormonal therapies and other adjuvant therapies, for example monoclonal antibodies, become more common, it may be increasingly important to examine whether women who are obese receive guideline-recommended adjuvant therapies of this type. Investigating receipt of these treatments according to BMI category would be particularly relevant, as well as challenging, in light of some evidence suggesting that some endocrine therapies may be less effective, as currently prescribed, among women with higher BMI.[25] Thus, future research in this domain should be interdisciplinary, incorporating a rigorous examination of patterns of care according to existing guidelines in tandem with consideration of whether the existing guidelines fully account for factors such as a potential need for higher doses of these therapies, or different combinations of therapies, to ensure maximum benefit in obese patients. Another aspect of hormonal therapy that will be particularly important to consider will be adherence to this treatment. Guidelines for hormonal therapies such as tamoxifen recommend that patients take these medications for 5 years or more after initial treatment is concluded to decrease the likelihood of recurrence; however, adherence to these regimens is frequently low.[119,127,128] To be comprehensive, researchers designing future studies could benefit from finding ways to investigate determinants of adherence or non-adherence to hormonal therapies as well as

initiation or non-initiation. Existing research suggests a major determinant of adherence is the experience of difficult side effects;[119,127] it would be productive to examine whether these side effects occur differentially between obese and non-obese women, and if possible to determine whether obese women receive similar amounts of support in dealing with these side effects. Some therapies, such as metformin (which has been found to decrease cancer mortality among cancer patients with Type II diabetes, and may become a part of comprehensive treatment for patients with this condition),[129] may be particularly salient to patients who are obese.

Underrepresented populations

Although our study population was diverse in many ways, there were some breast cancer patients who were not represented, including male breast cancer patients and women with less common subtypes of breast cancer (for example, lobular carcinoma *in situ*). Future research examining pathways connecting obesity and outcomes should include, if possible, members of these underrepresented patient groups, although this could be challenging in studies focusing on guideline adherence, since guidelines may not cover these patient populations.

Shared decision-making

We have alluded to the idea that obesity may have an impact on decision-making in cancer treatment. In this study, we did not (and could not) assess the extent to which choices about specific treatments were made through a process of shared decision-making in which patients were given adequate information and encouraged to take an active part in planning the course of therapy, as opposed to being in a more passive role or having their opinions or preferences discounted. These questions were not within the scope of this study, but are important to consider going forward in research focusing on receipt of appropriate care among individuals who are at high risk for poor outcomes after a cancer diagnosis.

Quality of life considerations

As mentioned previously, the NCCN guidelines are intended to improve not only patients' survival after a breast cancer diagnosis, but to reflect a balance between decreased mortality risk and acceptable quality of life. In our study, we were unable to address the question of how obese women's experiences compared with those of non-obese women in terms of quality of life during and after treatment; however, this is an important and increasingly relevant question, and one that would be a valuable addition to future research studies. In addition, future research aiming at understanding the relationship between guideline treatment and survival could include an assessment of whether and how receipt of guideline-concordant treatment contributes to quality of life among women with breast cancer.

Conclusion

In summary, this examination of patterns of care and mortality among women with invasive breast cancer resulted in several findings that were contrary to hypotheses advanced at the outset of the study. Higher body mass index was associated with greater hazard for breast cancer mortality only among women with Stage I disease, and it was actually inversely associated with overall mortality hazard among older women (with no relationship to mortality among women under 70). The apparent protective effect of higher BMI in regard to overall mortality in older women suggests that future research should carefully consider the role of BMI as women age and the possibility that its implications may be different among women who are older or younger at the time of breast cancer diagnosis. The expected pattern of breast cancer treatment according to BMI was also not observed; instead, women with higher BMI were at a moderate advantage in terms of likelihood of overall guideline-concordant treatment as defined in this study. While these findings should be considered in light of non-trivial limitations in the means of assessing

treatments received – primarily the low degree of granularity in measuring treatment within each therapeutic domain – to the extent that guideline concordance can be viewed as a meaningful indicator of a high standard of care in cancer treatment, these results indicate that in the population studied, obese women were not less likely to receive appropriate care. Guideline-concordant treatment also did not appear to be a mediator in the relationship between BMI and mortality among women with breast cancer. Taken together, these findings suggest that factors other than treatment are more important in the relationship between body size and breast cancer outcomes, although additional research investigating the treatment-related pathway is warranted. Future research including a longer follow-up period will be important in assessing the relationship between body size, treatment patterns, and mortality after a breast cancer diagnosis, as will studies incorporating greater detail on the treatment women receive for their breast cancer. Another valuable direction for future research would be a qualitative assessment of the decision-making process behind breast cancer treatment choices. Finally, future study designs should attempt to characterize not only mortality but also quality of life among women with differing body sizes, and investigate how clinical guidelines may affect women's quality of life during and after breast cancer treatment.

APPENDIX A: Conceptual Framework

A detailed version of the conceptual framework underlying this thesis is presented below. Unlike the simpler version presented in the Methods section (Chapter 3), this framework includes among the hypothesized contributors to the relationships between body size, guideline-concordant treatment, and mortality some factors that are outside the scope of this project but nonetheless represent potentially important pathways (e.g., breast cancer screening patterns and details of the tumor microenvironment). Relationships investigated in the study Aims are highlighted through the use of wider arrows.

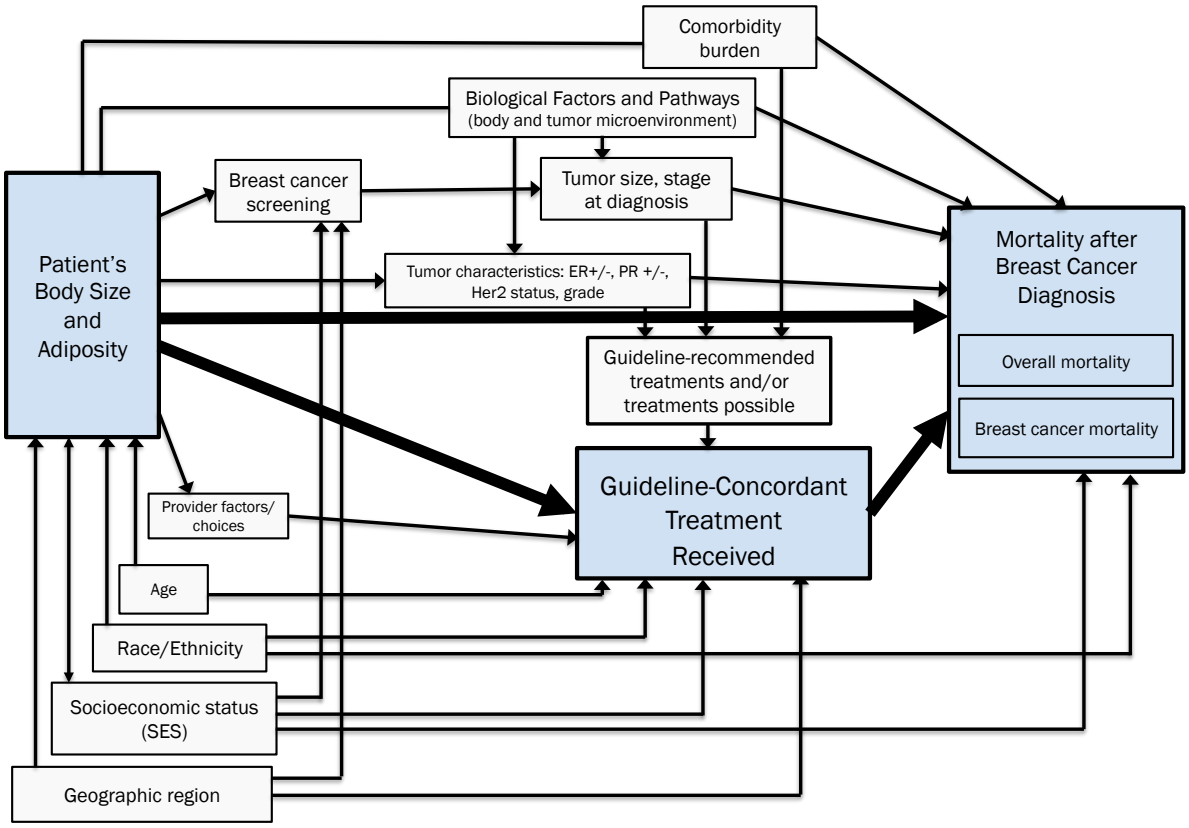

Figure A1. Detailed Conceptual Framework.

The components of our conceptual framework can be loosely grouped into 3 categories: (1) Patient demographic characteristics (which we consider mostly in the context of adjusting for potential confounders); (2) Comorbidities and biological factors/pathways related to tumor growth and development; and (3) Human factors related to the structure of health care and/or the behavior of patients and providers. These categories are discussed separately below.

Patient Demographic Characteristics

Among the patient characteristics described in our conceptual model, age is one of the most critical components in predicting both guideline-concordant treatment receipt and mortality from all causes or from breast cancer. While logic dictates that women who are older at the time of diagnosis will have a shorter average time to death, this is not the only way in which age at diagnosis relates to mortality, as women diagnosed at a younger age are more likely to have aggressive, unfavorable tumor subtypes.[2,52] Thus, it is important to consider that the potential confounding effects of age may work in differing ways across the age spectrum.

A full conceptual model describing the association between BMI and mortality must also include race and socioeconomic status (SES), both known to be closely associated with body mass index. The possibility that patients' race or SES may affect screening patterns as well as treatment is itself an important research priority given widely observed disparities in outcomes along racial and socioeconomic lines, and has been investigated elsewhere in the context of breast cancer treatment, with findings suggesting women who are members of racial minority groups or who have lower SES may indeed be less likely to receive adequate treatment.[118,130,131] Accurately capturing patients' race and SES and adjusting for these factors is a critical and potentially challenging part of examining a possible independent association between BMI and patterns of care as well as investigating the BMI-mortality connection. Insurance status (whether

one has insurance, and what type) is also an important potential determinant of the care an individual receives, one frequently but not always tied closely to SES. It can also be an indicator of higher risk for poor outcomes; for example, women who are dual-eligible for Medicare and Medicaid are a particularly high-risk population.

Geographic variations in screening and treatment have also been widely documented,[87,125,132] and breast cancer outcomes also differ according to a woman's area of residence.[133] The POC-BP study included a geographically diverse set of states, allowing for an examination of treatment patterns and outcomes related to geographic area; however, in the present analysis we were mainly concerned with taking geographic area into account due to its potential to be a confounder (since mean BMI also differs substantially according to area of residence).

Comorbidities and Biological Factors

Higher BMI is associated with higher risk of chronic disease, which would naturally contribute to higher all-cause mortality after a cancer diagnosis. The presence and type of comorbidities can also influence the range of options recommended by guidelines for cancer treatment. Beyond the effect of specific comorbidities on the range of guideline-recommended treatment options, comorbidity burden may be related to likelihood of receiving guideline-concordant care, although there are some differences between studies on addressing this question as to the direction of the relationship. Some research suggests that among patients in the general population, a higher level of "clinical complexity" (defined as a higher number of conditions and/or conditions that are more resource-intensive) is associated with a higher likelihood of receiving treatment that meets guidelines or performance measures.[134,135] However, other findings specific to patients with breast cancer (including results of a study conducted with the

POC-BP data set) indicate that women with a greater overall comorbidity burden are more likely to be under-treated[120] and less likely to receive guideline-concordant care.[83]

Similarly, the biological risk factors and pathways that are associated with adiposity may predispose obese patients toward having larger tumors and less favorable clinical tumor characteristics, which in turn will influence the treatment recommended for these patients as well as their likelihood of mortality. A number of physiological pathways are thought to drive part of the relationship between obesity and breast cancer recurrence and mortality; these are discussed in the Introduction, but we cover them in slightly more detail here.

Estrogen, insulin, and other endocrine pathways

Levels of adipose tissue are tied to a number of molecular and cellular changes in the body as a whole and in the breast tissue that can initiate, sustain, and promote breast tumor progression. Of these, endocrine changes, especially those related to estrogen and insulin pathways, appear to be among the most influential contributors.[48,52,136] Higher levels of adipose tissue in the body result in an increased rate of aromatization of androgen hormones, resulting in more circulating estrogen; this increase in estrogen levels is compounded by the fact that adipose tissue appears to decrease the liver's production of sex-binding hormone globulin (SBHG), leaving more of the produced estrogen circulating freely. Similarly, higher levels of adipose tissue within the breast lead to higher estrogen levels locally in the breast tissue. Increased estrogen from both sources promotes breast tumor growth.[52] Adiposity is associated with increased insulin synthesis, which promotes tumor growth and development.[52,136] Increased insulin levels also have indirect effects, as elevated insulin leads to higher levels of insulin-like growth factor 1 (IGF-1), which regulates genes involved in DNA repair and tumor proliferation and may also stimulate production of vascular endothelial growth factor (VEGF), a molecule known to exert a powerful pro-

angiogenic effect, thus supporting the vascularization and growth of tumors once they are established.[48,136] It should be noted that some research suggests the association between obesity and hyperinsulinemia appears to be stronger among women with adipose tissue concentrated more in the upper body,[137] a distinction not captured by BMI. Obese individuals also tend to have lower levels of serum vitamin D, a hormone precursor which has been found to be inversely associated with breast cancer mortality,[54] likely due in part to the role of its derivatives in triggering apoptosis in cancer cells.[138]

Inflammation

Chronically higher levels of inflammation, strongly associated with obesity, are tied to overall mortality, but also influence tumor growth.[48,52] Proinflammatory cytokines, such as interleukin-6 (IL-6) contribute to tumor progression directly; but chronic inflammation related to obesity may also contribute to differences in gene expression in adipose stem cells, making these cells more likely to act within the tumor microenvironment to promote tumor survival.[53]

Adipokines

Adipokines including leptin and adiponectin may also be involved in causal pathways linking obesity and breast cancer mortality.[48,52,136] More adipose tissue leads to higher levels of circulating leptin, which has systemic effects on immune function, cytokine production, and angiogenesis, as well as local effects on tumor survival, invasion, and proliferation resulting from its action on leptin receptors on breast cancer cells. Decreases in circulating adiponectin related to higher adiposity also have broad-reaching effects, as one of its functions is to regulate insulin and IGF-1. Notably, one study focusing on the relationship between BMI and breast cancer outcomes reported that in analyses adjusting for leptin levels, BMI was no longer significantly related to distant disease-free survival or overall survival.[136] This highlights leptin-

related pathways as critical potential mechanisms in the relationship between adiposity and mortality, but also potential confounders (when we consider that leptin levels may be elevated in lean individuals).

The complexity of the relationships between body shape and adiposity and various biological mechanisms (some clearly causal, some correlational) highlight the need to find meaningful and useful ways of characterizing bodily characteristics in research and treatment. Our use of BMI was an imperfect proxy, and as we discuss elsewhere, our results must be considered in light of some limitations that using BMI entails.

Human (Behavioral/Structural) Factors

In addition to patients' demographic and biological characteristics, our conceptual framework for relationships between BMI, treatment, and mortality after breast cancer includes a third set of variables, which we have described as structural and/or behavioral factors, but which could also be characterized as human factors. These include elements of the health care environment as well as patterns of decision-making by providers and patients.

Breast cancer screening and diagnosis

As previously mentioned, women with higher BMI tend to present with larger tumors at the time of diagnosis. This is likely in part related to more rapid tumor growth,[6,11,17] but this issue of faster tumor growth may be compounded by a lower likelihood of appropriately frequent screenings. Several studies have found that obese women are less likely to receive age-appropriate cancer screenings,[58,59,139-141] and that this may be due to weight-related barriers, including weight bias, in health care settings.[139,141] A study by Wee and colleagues indicated that this association between BMI and screening patterns may differ according to race.[58] More infrequent screening can result in delayed detection of tumors, and thus tumors that are larger at

the time they are detected. In addition, tumors detected by mammographic screening often differ from tumors detected by other methods. Reeves et al found an association between higher BMI and higher likelihood that a tumor was non-localized at diagnosis among women who detected tumors themselves, but not among women whose tumors were diagnosed during mammographic screening.[142]

Screening and diagnostic imaging in response to any abnormal findings can also present technical challenges, and be less accurate, among women who are obese.[60,143] Screening mammography, often the first step in the breast cancer detection process, can be less effective in obese women for technical reasons: larger breasts and an abdomen with more insulating fat tissue can make it difficult to obtain a high quality image from all desired angles, and it may not be possible to include all the tissue to be examined in a single image, necessitating the use of "tile" or "mosaic" imaging, which is not as helpful, particularly for comparisons over time. Issues related to a woman's body size may also emerge in subsequent steps in the diagnostic work-up process. Stereotactic biopsies tend to have a lower likelihood of success in larger women. In the ultrasound process, the thick breast tissue that tends to be present among obese women can require the use of a different transducer, with the result that the image produced is of lower-than-usual resolution.[60] Obtaining an accurate MRI can also be more challenging among obese women due to structural issues, some as basic as tables with weight limits lower than a woman's body weight, and some much harder to address, such as machines with a gantry size too small to accommodate the area to be imaged.[55,60]

Treatment challenges

Once diagnosed, obese women may be at risk for poorer treatment outcomes due to technical challenges related to their body size as treatment is delivered. Surgery may be more technically

difficult,[144] and it has been found that due to the difficulty involved in performing more radical or extensive surgeries on obese women, as well as the statistically higher risk of perioperative complications, these procedures may be less likely to be done in larger women even when appropriate.[52] Delivery of external radiation therapy can be more complicated in obese patients;[145,146] obesity has been found to be associated with a higher number of setup errors and the need for a larger margin around the site of delivery.[145] In addition, existing literature suggests that some systemic therapies (even when given at what is currently considered a correct dose) may be less effective in obese patients,[14,25,144,147,148] although evidence for this possibility is not conclusive.

Differences in treatment resulting from provider knowledge and attitudes

Provider attitudes and knowledge could affect treatment decisions, and thus treatment outcomes, in several ways, not all direct. It is possible that simple weight-based bias may contribute to suboptimal treatment among obese women; weight bias is known to be an issue in medical care,[139,149] although most research documenting this issue has focused on primary care settings. This bias, characterized by physicians or other providers consciously or unconsciously harboring negative perceptions of obese patients and frequently treating these patients differently than "normal-weight" patients for this reason, has been widely documented among providers of primary care, although the extent to which this suboptimal treatment leads to worse outcomes has not been clearly established.[139,149] While similar studies focusing explicitly on obesity appear not to have been conducted in the oncology setting, some research has indicated that oncologists' decision-making is often significantly affected by non-clinical patient factors, such as the physician's assessment of a patient's ability to follow directions or the level of social support the

patient is perceived to have.[150] Overall, however, little is known about whether providers working in specialized settings such as oncology treat patients differently due to negative perceptions based on their weight. If such bias did exist, its effect could manifest in actions such as treating an obese patient as if she had a lower likelihood of tolerating, benefitting from, or adhering to treatments. Also concerning is the possibility that the process of shared decision-making in planning the course of treatment could be impaired by a provider's unconscious bias toward obese patients, even a patient's own lowered expectations of providers' respect for her opinions, built up through years of negative experience in other health care settings.

Even in the absence of any biased attitudes, the physician's part of the decision-making process could be compromised by a lack of knowledge or agreement among providers about appropriate treatment for obese patients. Randomized controlled trials, considered the bedrock of most evidence-based medicine, may exclude very obese patients, leaving a less firm knowledge base. Even when strong evidence suggests obese patients should be treated in the same way as their non-obese counterparts, as in the case of full body weight-based chemotherapy dosing, physicians may be hesitant to reject the notion of obese patients as in a separate category, likely a higher-risk category. The very fact that providing equivalent treatment for obese patients may sometimes entail going outside of their accustomed practice patterns – for example, using a different strategy when doing imaging, or prescribing a chemotherapy dose that is higher than they are used to providing – could make this equivalency less likely to happen in practice. There have been, to our knowledge, no formal studies of physicians' feelings and beliefs about the recommendation for full weight-based chemotherapy, but one of the ASCO guidelines' authors has described conversations with providers in which they expressed the discomfort and even fear they felt when prescribing doses as high as the actual body weight based calculations would

dictate,[151] and other researchers have also described physicians' concerns about the impact of actual body weight based chemotherapy.[129] It is possible that, in marginal cases, oncologists might take concerns over the difficulty of appropriate dosing into account when deciding whether or not to initiate chemotherapy as well.

As the multitude of factors included in the conceptual model indicates, a provider's thoughts and attitudes when planning a patient's treatment are by no means the only determinants of the treatment that patient eventually receives, and examining factors driving decision-making for physicians, or indeed for patients, is beyond the scope of this analysis. However, the process of shared decision-making in breast cancer screening and treatment, driven as it is in large part by the attitudes providers and patients hold, is an area in which there is substantial room for improvement in general, and would be a fruitful area of focus for future research investigating potential effects of body size on processes intended to maintain breast health.

APPENDIX B: Missing Weight and Height According to Demographic and Clinical Characteristics

Of Stage I, II, or III breast cancer patients who were otherwise eligible for inclusion in the study sample, records for 1462 out of 6862 (21.3%) were missing weight and/or height information, precluding the calculation of body mass index (BMI). 596 patients (8.7%) were missing only height information, 59 (0.9%) were missing only weight information, and 807 (11.8%) were missing information on height and weight. Possible bias in our findings resulting from associations between BMI missingness and patient characteristics was a concern; for example, in attempting to model relationships between BMI and mortality, there would be a risk of unreliable results if women were at higher risk for mortality (e.g., women who were older at time of diagnosis, or who had unfavorable tumor characteristics) were also more likely to have missing BMI.

We attempted to address this concern in multiple ways. As an initial step, we assessed whether missing height and/or weight information – hereafter referred to, for simplicity, as "missing BMI" – was more frequent among women with important demographic and/or clinical characteristics. Age-adjusted linear regression models were used to compare the proportion of patients with missing weight and/or height across basic treatment categories (e.g., receipt/nonreceipt of radiation therapy; enrollment/non-enrollment in a clinical trial) and across explanatory variables used in our proportional hazards and logistic regression analyses for all Aims. (Another approach used to address, at least in part, the missing information issue was multiple imputation; the resulting findings are described in Appendix C.)

Demographic Variables Associated with Missing BMI (Table B1)

Patients in higher age categories were more likely to have missing BMI information ($p < 0.001$). BMI was missing among roughly a quarter (24.8% to 27.7%) of women age 70 or older, compared to 19.5% or fewer of women below age 70. In age-adjusted analyses, several other demographic and clinical factors were also associated with likelihood of BMI information being missing. Patients categorized as American Indians or Alaska natives were the most likely on average to have missing BMI (29.5% with missing BMI); white patients were the second most likely, and black patients third most likely, compared to Hispanic and API patients, both of which categories had < 17% with missing BMI. These differences by racial category were significant ($p < 0.001$), although there were a small number of American Indian/Alaska Native patients ($n = 59$). Patients' insurance type also showed a significant association with likelihood that BMI information was missing ($p = 0.004$). Those patients who had no insurance or who had Medicare or other public insurance only were somewhat more likely to have missing BMI information (24%) compared to patients with private insurance or Medicaid (19%), but by far the largest proportion of patients with missing BMI was found among patients for whom insurance information was also missing (30%).

Patients living in a lower-education census tract were not significantly more likely to have missing BMI compared to those living in a higher-education census tract ($p = 0.54$); similarly, patients living in a higher-poverty census tract were not significantly more likely to have missing BMI compared to those living in a lower-poverty census tract ($p = 0.68$). A higher proportion of patients living in rural or mixed urban-rural areas had missing BMI values compared to patients living in urban areas (23-25.5% versus 18.1%,

$p < 0.001$ for overall difference) and the proportion of patients with missing BMI information also varied substantially by tumor registry, from 13.4% to 36.8% ($p < 0.001$).

Clinical Variables Associated with Missing BMI (Table B2)

A higher proportion of patients with missing BMI was found among patients with stage I disease (22.1%) than among women with tumors staged as II (19.1%) or III (21.4%), although the relationship was of only borderline statistical significance ($p = 0.09$). Tumor size was not related to likelihood that BMI information was missing ($p = 0.72$); nor was tumor grade ($p = 0.55$). Patients with no comorbid conditions were more likely to have missing BMI information ($p < 0.001$), as were women with no positive lymph nodes ($p = 0.04$). Unknown status of estrogen receptors (ER) and human epidermal growth receptor 2 (Her2-neu) were associated with greater likelihood of having missing BMI information; as was the case with insurance information, patients with unknown values for the variable of interest (31.5% and 28.7% for patients with unknown ER and Her2-neu, respectively), were more likely to have missing BMI information compared patients with known positive or known negative status either receptor type (18%-21%). A higher proportion of women with missing BMI was found among women with unknown PR status (26%) compared to women with known positive status (21%) or negative status (19%); however, this association was not significant ($p = 0.64$).

Treatment Variables Associated with Missing BMI (Table B3)

Patients who received chemotherapy were substantially less to be missing BMI information in their records compared to those who did not receive chemotherapy (17.9% versus 23.4%), as would be expected given the importance of body weight in determining chemotherapy dose; patients who refused chemotherapy, or whose medical records

indicated chemotherapy was not given due to contraindications, were even less likely to have missing BMI information (15.5-16%); and the proportion with missing BMI among patients for whom chemotherapy information was missing altogether was 18.4% (p-value for the association with chemotherapy status as a whole = 0.01).

Recipients of radiation therapy and hormone therapy were also less likely to have missing BMI than non-recipients, and women whose medical records indicated these treatments were contraindicated or refused by the patient were substantially more likely to have missing BMI; women with missing information on radiation therapy or hormonal therapy receipt were, in particular, more likely to have missing BMI (p-value for overall pattern = 0.03 for radiation therapy, $p < 0.001$ for hormonal therapy).

Information on enrollment in a clinical trial was also strongly associated with presence of BMI information. Among women recorded as being enrolled in a trial, BMI was missing for 17.2%, and among women recorded as not being enrolled in a trial BMI was missing for 20.1%, but among those with no information on trial enrollment status, BMI was missing for 42.9% (p-value for the association as a whole < 0.001).

Our reasons for investigating potential systematic patterns of missing information used to calculate BMI were primarily related to concerns about potential bias. We discuss our findings in the context of research Aims 1 and 2 separately below.

Results from our Aim 1 and Aim 3 analyses (related to mortality) could be called into question by a pattern of higher likelihood of missing BMI among women with characteristics generally associated with more favorable, or less favorable, outcomes. While we did observe some patterns, they were inconsistent with regard to the association between missing BMI and favorable or unfavorable prognostic characteristics. Women

who were older, a group clearly at greater risk for mortality after a breast cancer diagnosis, were more likely to have missing BMI; however, a greater probability of missing BMI information was also found among women with a lower tumor stage, as well as those with a greater comorbidity burden at the time of diagnosis, both predictors of lower mortality.

For our Aim 2 and Aim 3 analysis results, bias could be an issue if women more likely to have missing weight and/or height information were also more likely to have characteristics associated with guideline treatment receipt. To a certain extent, this was the case. Across the treatment domains and with regard to overall guideline-concordant treatment, the covariates most consistently found to relate to likelihood of guideline-concordant treatment were age, insurance type, and tumor size. As noted above, older women were more likely to have missing BMI, and older age was also generally associated with lower likelihood of receiving guideline-concordant treatment; patients with types of insurance associated with lower likelihood of guideline treatment receipt were also more likely to have missing BMI information.

Table B1. Missing BMI by Patient Demographic Characteristics, POC-BP, 2004

Patient Characteristic	N[1]	Percent with Missing BMI		
		%	SE	p-value[2]
Age				
< 40	479	15.9	1.1	< 0.001
40-49	1528	18.6	1.1	
50-59	1775	18.6	1.0	
60-69	1413	19.5	1.1	
70-79	1107	24.8	1.2	
≥ 80	560	27.7	1.6	
Race				
White, non-Hispanic	3974	21.7	0.6	< 0.001
Black, non-Hispanic	1851	19.8	1.3	
AI/AN, non-Hispanic	59	29.5	0.9	
API, non-Hispanic	378	16.3	2.7	
Hispanic	597	14.9	2.0	
Insurance				
Private	3993	19.0	0.7	0.004
Medicare/other public	1490	24.1	1.2	
Medicaid	948	19.1	1.6	
None	198	24.3	3.4	
Unknown[3]	233	30.3	2.4	
Census-tract education				
Higher	4182	20.6	0.6	0.54
Lower	2660	21.4	0.9	
Census-tract poverty				
Lower	5135	21.4	1.2	0.68
Higher	1707	20.8	0.6	
Urbanicity				
Urban	3434	18.1	0.7	< 0.001
Urban/Rural mixed	2406	23.0	0.9	
Rural	1003	25.5	1.3	
Registry (State)				
1	781	23.6	1.2	< 0.001
2	781	36.8	1.4	
3	686	16.0	0.1	
4	412	21.4	1.6	
5	1327	26.7	1.6	
6	1591	17.2	1.2	
7	1284	13.4	1.0	

Abbreviations: AI/AN, American Indian/Alaska Native; API, Asian/Pacific Islander

1. Numbers may not total to 6,859 for all categories to missing data (not listed as "unknown") on patient demographic characteristics for some (< 21) women.
2. p-value from general linear model (PROC SURVEYREG) comparing means between categories, adjusted for age. Means from general linear model produced using PROC GLM with option for weighting.
3. A separate analysis excluding women with unknown insurance type showed that insurance category was still associated with missing BMI, albeit with borderline statistical significance (p = 0.06).

Table B2. Missing BMI by Patient Clinical Characteristics, POC-BP, 2004

Clinical Characteristic	N[1]	Percent with Missing BMI		
		%	SE	p-value[2]
Tumor stage (AJCC)				
I	3230	22.1	0.8	
II	2592	19.1	0.8	0.09
III	1040	21.4	1.3	
Tumor Size				
≤ 0.5 cm	570	20.2	1.7	
0.51 - 1 cm	1073	22.0	1.3	
1.01 - 2 cm	2065	21.4	0.9	0.72
2.01 - 5 cm	2548	19.9	0.8	
> 5 cm	526	21.1	1.9	
Unknown[3]	80	26.9	4.4	
Lymph Nodes				
Any positive	2375	18.2	0.9	0.04
All negative	4129	20.9	0.7	
Grade				
I (well differentiated)	1205	21.3	1.2	
2 (moderately differentiated)	2625	21.0	0.8	
3 (poorly differentiated)	2575	20.9	0.9	0.55
4 (undifferentiated)	74	14.5	5.1	
Unknown[4]	383	18.9	2.2	
Comorbidity				
None	3180	24.5	0.8	
Mild	3010	18.2	0.8	< 0.001
Moderate	461	14.1	1.9	
Severe	211	16.3	2.8	
ER Status				
Positive	4773	20.8	0.6	
Negative	1738	18.7	1.0	0.006
Unknown[5]	351	31.5	2.2	
PR Status				
Positive	4005	21.1	0.7	
Negative	2426	19.4	0.9	0.64
Unknown[6]	431	25.9	1.9	
Her2-neu Status				
Positive	2335	18.3	0.9	
Negative	3318	19.8	0.7	< 0.001
Unknown[7]	1209	28.7	1.2	

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor 2 receptor.

1. Numbers do not total to 6,862 for lymph node category comparison; lymph node status was missing for 358 women and not coded as "unknown."

2. p-value from general linear model (PROC SURVEYREG) comparing means between categories, adjusted for age. Means from general linear model produced using PROC GLM with weighting option.

3. A separate analysis excluding women with unknown tumor size also showed that tumor size was not associated with missing BMI (p = 0.78).

4. An analysis excluding women with unknown tumor grade also showed grade was not associated with missing BMI (p = 0.48).

5. An analysis excluding women with unknown ER status showed that ER status was *not* statistically significantly associated with missing BMI (p = 0.12).

6. An analysis excluding women with unknown progesterone receptor (PR) status also showed that tumor size was not associated with missing BMI (p = 0.78).

7. An analysis excluding women with unknown Her2-neu status showed that Her2-neu status was *not* associated with missing BMI (p = 0.25).

Table B3. Missing BMI by Treatment Type, POC-BP, 2004

Treatment	N	Percent with Missing BMI		
		%	SE	p-value[1]
Chemotherapy[2]				
Yes	3448	17.9	0.8	
No	2902	23.4	0.8	
Contraindicated	73	15.5	4.5	< 0.001
Refused by patient	263	16.0	2.4	
Unknown[3]	47	18.4	6.2	
Radiation therapy				
Yes	3879	19.6	0.7	
No	2580	21.1	0.8	
Contraindicated	62	26.9	5.0	0.03
Refused by patient	170	26.7	3.1	
Unknown[4]	171	32.6	2.9	
Hormonal therapy				
Tamoxifen/AIs	3511	19.6	0.01	
Any other	90	14.6	0.04	
No	2759	20.4	0.01	< 0.001
Contraindicated	56	26.0	0.05	
Refused by patient	161	26.8	0.03	
Unknown[5]	285	35.1	0.02	
Enrolled in Clinical Trial				
Yes	291	17.2	2.2	
No	6372	20.1	0.6	< 0.001
Unknown[6]	199	42.9	2.5	

Abbreviations: AIs, aromatase inhibitors.

1. p-value from general linear model (PROC SURVEYREG) comparing means between categories, adjusted for age. Means are from a general linear model produced using PROC GLM with option for weighting.

2. Numbers do not total to 6,862 for chemotherapy comparison; chemotherapy information was missing for 129 women and not coded as "unknown."

3. A separate analysis excluding women with unknown chemotherapy receipt also showed that chemotherapy decision was associated with missing BMI ($p < 0.001$).

4. A separate analysis excluding women with unknown radiation therapy (RT) receipt showed that RT decision was not associated with missing BMI ($p = 0.22$).

5. A separate analysis excluding women with unknown hormonal therapy (HT) receipt showed that HT decision was no longer associated with BMI ($p = 0.27$).

6. A separate analysis excluding women with unknown clinical trial enrollment status showed clinical trial enrollment was not associated with BMI ($p = 0.29$).

APPENDIX C: Aim 1 Extra Tables and Sensitivity Analyses

This Appendix covers the following analyses:

Test of the Proportional Hazards Assumption
Body Weight Analyses (Alternative to BMI) - Tables C1 and C2
Spline-Based Models – Figures C1a-C1d
Models Using Multiple Imputation – Tables C3a and C3b
Recursive Partitioning (Regression Trees) – Figures C2a-C2c, Tables C4a and C4b
Models Using Vital Status Censored at 5 Years – Table C5

Testing Proportional Hazards Assumption

In using Cox regression models for our survival analyses modeling overall mortality and breast cancer mortality on BMI (and other covariates), we made the assumption that the association between BMI and hazard of overall or breast cancer-specific mortality did not vary according to time since diagnosis. We tested this proportional hazards assumption by incorporating a term representing an interaction between BMI and time since diagnosis into our original models and assessing the significance of the coefficient. The BMI-by-time term was not found to be significant in models for overall mortality ($p = 0.38$) or for breast cancer mortality ($p = 0.58$); therefore, we concluded it was appropriate to operate under the assumption of proportional hazards.

Alternative Characterizations of Body Size/Adiposity

Body Weight instead of BMI

As mentioned in Appendix B, we were not able to calculate BMI for a substantial number of women who were otherwise eligible for inclusion in analyses (1462 women, 21.3% of those

otherwise eligible). This analysis partially addressed the missing information issue by examining whether overall or breast cancer survival was associated with body weight, since weight was missing less frequently than height, and reflects BMI fairly well for at least the upper portion of the scale. In sensitivity analyses focused on body weight as an alternative to BMI, we first calculated hazards ratios for overall mortality and breast cancer-specific mortality in the group of women used for the analytic data set in our Aim 1 analyses (Table C1), and then ran the same models using the slightly larger analytic data set comprising all women with known body weight (Table C2). Including all women with known body weight rather than those with known BMI added 578 women to the group available for analysis, leaving an analytic data set of 5792 women, among whom the proportion of women known to be deceased at 8 years was 19.2% (the same percentage as in Aim 1 analyses shown in Chapter 4). Results from these analyses are presented below, with a copy of the corresponding table from Chapter 4 (Table 3) included for ease of reference.

Table C1 shows results of proportional hazards regression models investigating the relationship between body weight and all-cause or breast cancer-specific mortality in the set of women used for the analytic data set in our Aim 1 analyses; these results are primarily of academic interest, since unlike those in Table C2, they do not actually reflect a larger analytic data set. Hazards ratios were calculated for different body weight categories in comparison to a reference category, and for a 10-pound difference in body weight (for context, a difference in 10 pounds of body weight for a woman 5'7" in height corresponds to roughly a 1.5 kg/m^2 difference in BMI). As observed in our Aim 1 analyses of BMI and mortality, greater body weight was associated with lower mortality from any cause (HR for a difference of 10 pounds = 0.98, 95% CI 0.96 – 1.00, p = 0.04), but body weight was not associated with mortality due to breast cancer. Table C2 shows

results of the same models, using body weight and measuring all-cause and breast cancer-specific mortality among all women with known body weight. These results also mirror those from the Aim 1 analyses: a trend was observed suggesting that higher body weight was associated with lower overall mortality, although it was of only borderline statistical significance ($p = 0.07$), and body weight was not associated with breast cancer mortality.

Included for Reference:

Table 3 from Paper 1 ("Obesity and Mortality After Locoregional Breast Cancer Diagnosis")

Table 3. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for All-Cause Mortality and Breast Cancer-Specific Mortality According to Body Mass Index

Patient Characteristic	All-Cause Mortality			Breast Cancer-Specific Mortality		
	HR	95% CI	p-value for trend	HR	95% CI	p-value for trend
Model 1: Adjusting for Age and Tumor Stage (AJCC)						
Body Mass Index (kg/m^2)						
< 18.5	1.20	0.72 - 2.00		**0.37**	0.14-0.99	
18.5-24.9	1 (ref)			1 (ref)		
25-29.9	0.85	0.70 - 1.04	0.14	0.92	0.68 - 1.25	0.68
30-34.9	0.81	0.65 - 1.02		0.98	0.71 - 1.36	
≥35	0.93	0.73 - 1.19		0.95	0.67 - 1.36	
Age at Diagnosis (years)	1.05	1.04 - 1.05	< 0.001	1.00	0.99 - 1.01	0.996
Tumor Stage (AJCC)						
I	1 (ref)					
II	1.88	1.56 - 2.26	< 0.001	4.63	3.25 - 6.60	< 0.001
III	5.14	4.21 - 6.28		17.92	12.69 - 25.30	
Model 2: Adjusting for Age, Tumor Stage, and Other Clinical and Demographic Characteristics[1]						
Body Mass Index (kg/m^2)						
< 18.5	1.31	0.80 - 2.15		**0.33**	0.12 - 0.93	
18.5-24.9	1 (ref)			1 (ref)		
25-29.9	0.82	0.67 - 1.01		0.87	0.4 - 1.19	
30-34.9	**0.75**	0.59 - 0.95		0.94	0.68 - 1.30	
≥35	0.85	0.67 - 1.08		0.93	0.64 - 1.35	
per 5 kg/m2 Δ	**0.93** (0.87 - 0.95)		**0.02**	0.98 (0.94 - 1.02)		0.42
Age at Diagnosis (years)	1.04	1.03 - 1.05	< 0.001	1.00	0.99 - 1.01	0.91
Tumor Stage (AJCC)						
I	1 (ref)			1 (ref)		
II	1.62	1.34 - 1.95	< 0.001	3.36	2.33 - 4.86	
III	3.94	3.19 - 4.86		12.23	8.57 - 17.46	< 0.001

Abbreviations: AJCC, American Joint Commission on Cancer

1. Model 2 adjusted for age, tumor stage, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status, and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity.

Table C1. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for All-Cause Mortality and Breast Cancer-Specific Mortality According to Body Weight

Patient Characteristic	All-Cause Mortality			Breast Cancer-Specific Mortality		
	HR	95% CI	p-value	HR	95% CI	p-value
Model 1: Adjusting for Age and Tumor Stage (AJCC)						
Body Weight (lbs)[1]						
< 122	1.15	0.86 - 1.55		1.03	0.61 - 1.73	
122 - 140	1 (ref)			1 (ref)		
141 - 162	0.87	0.68 - 1.11		0.99	0.67 - 1.45	
163 - 193	0.86	0.67 - 1.09		1.06	0.73 - 1.54	
194 - 226	0.95	0.71 - 1.27		1.11	0.72 - 1.69	
≥ 227	0.86	0.62 - 1.19		0.80	0.50 - 1.26	
per 10 lb Δ	0.99	0.97 - 1.01	0.26	1.00	0.97 - 1.02	0.71
Age at Diagnosis (years)	1.05	1.04 - 1.05	< 0.001	1.00	0.99 - 1.01	0.93
Tumor Stage (AJCC)						
I	1 (ref)			1 (ref)		
II	1.87	1.55 - 2.25	< 0.001	4.64	3.26 - 6.60	< 0.001
III	5.14	4.22 - 6.27		17.97	12.76 - 25.32	
Model 2: Adjusting for Age, AJCC stage, and Other Clinical and Demographic Characteristics[2]						
Body Weight (lbs)[1]						
< 122	1.24	0.92 - 1.67		0.99	0.59 - 1.68	
122 - 140	1 (ref)			1 (ref)		
141 - 162	0.85	0.66 - 1.09		0.90	0.61 - 1.34	
163 - 193	0.83	0.64 - 1.06		0.99	0.68 - 1.46	
194 - 226	0.90	0.67 - 1.21		1.06	0.69 - 1.64	
≥ 227	0.76	0.55 - 1.06		0.77	0.48 - 1.22	
per 10 lb Δ	**0.98**	0.96 - 1.00	**0.04**	1.00	0.97 - 1.02	0.70

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Age at Diagnosis (years)	1.04	1.03 - 1.05	< 0.001	1.00	0.99 - 1.01	0.92
Tumor Stage (AJCC)						
I	1 (ref)			1 (ref)		
II	1.61	1.33 - 1.95	< 0.001	3.36	2.33 - 4.84	< 0.001
III	3.93	3.18 - 4.84		12.22	8.58 - 17.41	

Abbreviations: AJCC, American Joint Commission on Cancer

1. Body weight categories represent the following percentile ranges of weight among women included in analyses: 0-10, 10-25, 25-50, 50-75, 75-90, 90-100.

2. Model 2 adjusted for age, AJCC stage, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status, and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity.

Table C2. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for All-Cause Mortality and Breast Cancer-Specific Mortality According to Body Weight Among All Women with Stage I-III Breast Cancer With Known Body Weight (N = 5972)

Patient Characteristic	All-Cause Mortality			Breast Cancer-Specific Mortality		
	HR	95% CI	p-value	HR	95% CI	p-value
Model Adjusting for Age, Tumor Stage, and Other Clinical and Demographic Characteristics[1]						
Body Weight (lbs)[2]						
< 122 (n = 558)	**1.47**	1.12 - 1.93		1.16	0.74 - 1.82	
122 - 140 (n = 1052)	1.14	0.90 - 1.45		1.11	0.76 - 1.61	
141 - 162 (n = 1398)	1 (ref)			1 (ref)		
163 - 193 (n = 1517)	0.97	0.78 - 1.21		1.18	0.87 - 1.60	
194 - 226 (n = 871)	1.05	0.80 - 1.36		1.19	0.83 - 1.70	
≥ 227 (n = 576)	0.96	0.72 - 1.28		0.97	0.67 - 1.42	
per 10 lb Δ	0.98	0.96 - 1.00	0.07	1.00	0.98 - 1.03	0.95
Age at Diagnosis (years)	1.04	1.03 - 1.05	< 0.001	1.00	0.99 - 1.01	0.76
Tumor Stage (AJCC)						
I	1 (ref)			1 (ref)		
II	1.57	1.31 - 1.88	< 0.001	3.11	2.19 - 4.41	< 0.001
III	3.86	3.17 - 4.69		11.77	8.40 - 16.49	

Abbreviations: AJCC, American Joint Commission on Cancer

1. Body weight categories represent the following percentile ranges of weight among women included in Aim 2 analyses (Chapter 5): 0-10, 10-25, 25-50, 50-75, 75-90, 90-100.

2. Model 2 adjusted for age, tumor stage, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status, and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity.

Spline-Based Models

As an alternative means of characterizing potential non-linear trends with the potential for greater sensitivity to non-linear trends, we used natural cubic splines-based models to describe the hazard for mortality after a breast cancer diagnosis according to BMI. BMI was rounded to the nearest integer and hazard ratios were calculated for each integer value of BMI up through 50 kg/m^2, compared to a reference value of 22 kg/m^2.

Figure C1a depicts results relating to overall mortality, with estimated hazard ratios shown by a line and 95% confidence intervals (CIs) shown by gray bars above and below. A sharp curve is seen between the lowest BMI, 14 kg/m^2, and the BMI chosen as the reference group, with hazard ratios for all BMI values below 22 kg/m^2 being above 1.0, with 95% CIs not including 1, indicating a strong association between hazard for all-cause mortality and being underweight, or even having a BMI lower than 22 that is not characterized as underweight in the standard classification. Hazard ratio estimates for higher BMI values, as compared to 22 kg/m^2, are below 1.0, even up through 50 kg/m^2, although the 95% CIs begin to overlap 1 at 40 kg/m^2, making it hard to draw conclusions about the true shape of the BMI-mortality curve in this upper range. On the whole, results from the splines-based model are similar to our findings in the main analyses (Aim 1), although they more strongly illustrate a positive association between being underweight and the hazard for all-cause mortality.

Figure C1b shows results for overall mortality specifically among women age 70 or older (the group among whom overall mortality was found to be significantly inversely associated with all-cause mortality in our Aim 1 analyses, reported in Chapter 4). This graph's shape also illustrates a strong positive association between being underweight and hazard for all-cause mortality, while the seeming protective effect of higher BMI is less apparent. Women with

higher BMI did have lower hazard ratio estimates for the most part, but for BMI greater than 27 kg/m^2, the middle of the standard "overweight" range, the 95% CIs overlapped 1, and starting at a BMI of 44 kg/m^2, higher BMI was associated with HR estimates showing elevated mortality hazard (although still with 95% CIs including 1).

Figures C1c and C1d depict results from models of breast cancer mortality according to BMI among all women, and among women with Stage I disease only, respectively. As might be expected from our Aim 1 findings, aside from a slight indication of potentially elevated hazard for breast cancer mortality among those who are underweight, the graph for breast cancer mortality among all women (C1c) shows an essentially flat curve. In contrast, the graph for women with Stage I disease (C1d) shows a curve that is roughly flat in the 14-30 kg/m^2 range but then increases sharply before starting to level off; this curve, indicating a significantly elevated hazard for mortality among women in the upper BMI range, also reflects the same pattern observed in our findings from Aim 1 analyses, although the spline-based model allows for a more detailed understanding of the apparent shape of the relationship.

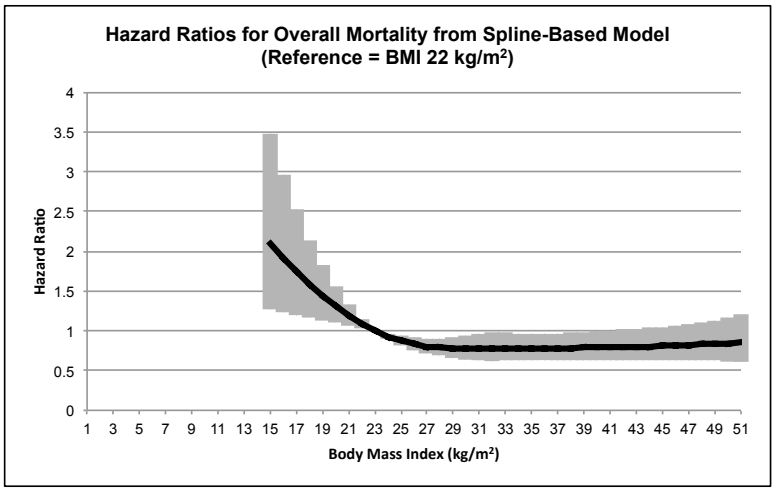

Figure C1a. Hazard ratios and 95% confidence intervals for overall mortality according to BMI from natural cubic spline models.

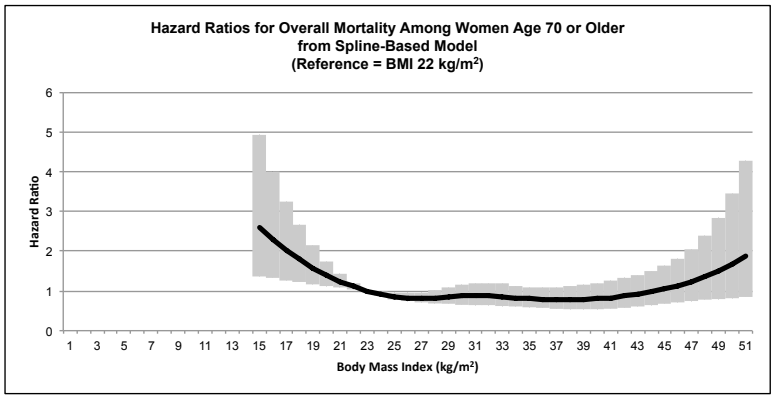

Figure C1b. Hazard ratios and 95% confidence intervals for overall mortality according to BMI, among women age 70 or older, from natural cubic spline models.

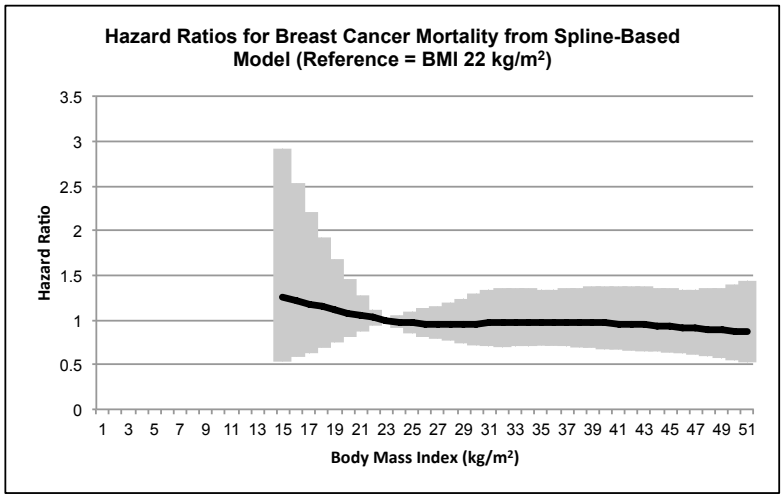

Figure C1c. Hazard ratios and 95% confidence intervals for breast cancer-specific mortality according to BMI from natural cubic spline models.

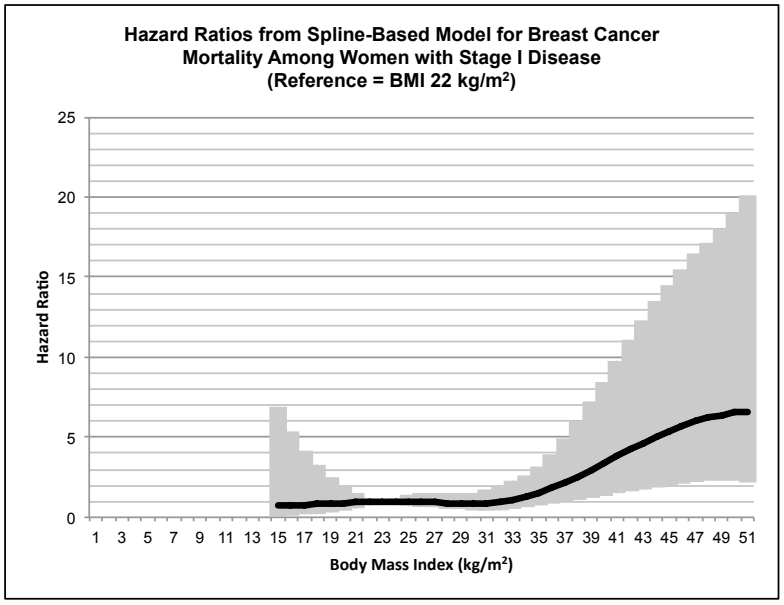

Figure C1d. Hazard ratios and 95% confidence intervals for breast cancer-specific mortality according to BMI, among women with Stage I disease, from natural cubic spline models.

Models Using Multiple Imputation

As a means of addressing questions of potential bias related to missing data, we employed a multiple imputation approach to estimate BMI among women with missing information on weight and/or height. 6,856 women were included in the data set with BMI estimated when necessary from imputed weight and/or height, as compared to 5,394 in the data set used for analyses in Paper 1. Tables C3a and C3b present results from regression models for overall and breast cancer mortality using the data set including women with BMI based on imputed values to those including only women with known BMI. The results from models focusing on overall mortality (C3a) were similar to findings reported in Paper 1 (Chapter 4), with lower hazard for mortality associated with higher BMI categories, although hazards ratios for each BMI category were for the most part closer to 1 (null findings), and the association between BMI and mortality was no longer statistically significant (HR for a 5 kg/m^2 difference in BMI = 0.97, 95 % CI 0.92-1.01, p = 0.13). Results from models focusing on breast cancer mortality (C3b), like those reported in Chapter 4, also showed no association between BMI and breast cancer-specific mortality among the group as a whole (p = 0.56).

Table C3a. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for All-Cause Mortality According to BMI, with Missing BMI Calculated from Imputed Weight and Height

Patient Characteristic		All-Cause Mortality (Missing BMI Excluded)[1,2]				All-Cause Mortality (Model with Imputed Values, N = 6,856)[1,3]		
		HR	95% CI	p-value		HR	95% CI	p-value
Body Mass Index (kg/m^2)	%				%			
< 18.5	1.5	1.31	0.80 - 2.15		2.4	1.43	0.98 - 2.08	
18.5-24.9	32.5	1 (ref)			29.0	1 (ref)		
25-29.9	30.3	0.82	0.67 - 1.01		29.5	0.94	0.81 - 1.09	
30-34.9	19.8	**0.75**	0.59 - 0.95		21.2	0.90	0.76 - 1.06	
≥35	15.8	0.85	0.67 - 1.08		17.9	0.93	0.78 - 1.11	
per 5 kg/m2 Δ		0.93	0.87 - 0.99	**0.02**		0.97	0.92 - 1.01	0.13

1. Model adjusted for age, tumor stage, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status, and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity.

2. Same model as presented in Table 2 of Paper 1 (Chapter 4); included here for comparison with the model using imputed values.

3. BMI, when missing, was calculated from imputed weight and height (PROC MI, SAS 9.3).

Table C3b. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for Breast Cancer-Specific Mortality According to BMI, with Missing BMI Calculated from Imputed Weight and Height

Patient Characteristic		Breast Cancer Mortality (Missing BMI Excluded) [1,2]				Breast Cancer Mortality (Model with Imputed Values, N = 6,856) [1,3]		
		HR	95% CI	p-value		HR	95% CI	p-value
Body Mass Index (kg/m^2)	%				%			
< 18.5	1.5	0.33	0.12 - 0.93		2.3	0.92	0.42 - 2.02	
18.5-24.9	32.5	1 (ref)			29.0	1 (ref)		
25-29.9	30.3	0.87	0.40 - 1.19		29.6	1.05	0.83 - 1.32	
30-34.9	19.8	0.94	0.68 - 1.30		21.2	1.18	0.93 - 1.49	
≥35	15.8	0.93	0.64 - 1.35		17.9	1.06	0.81 - 1.39	
per 5 kg/m2 Δ		0.98 (0.94 - 1.02)		0.42		1.01	0.96 - 1.08	0.56

1. Model adjusted for age, tumor stage, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status, and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity.

2. Same model as presented in Table 2 of Paper 1 (Chapter 4); included here for comparison with the model using imputed values.

3. BMI, when missing, was calculated from imputed weight and height (PROC MI, SAS 9.3).

Recursive Partitioning Approach (Regression Trees)

We conducted recursive partitioning analyses using R to identify characteristics that were important in determining the outcome of interest (all-cause mortality or breast cancer-specific mortality). In the recursive partitioning approach, data are split into homogeneous groups (groups with the most similar in terms of likelihood of experiencing the outcome of interest) on the basis of continuous or categorical explanatory variables; this occurs in an iterative process, with each split based on a rule based on a single explanatory variable.[152] The end result is a tree with "branches" showing the splits that occurred in the calculation process, nodes representing the intermediate groupings, and "leaves" or terminal nodes representing the final groupings (groups that are the most homogenous possible in a tree with a reasonable number of splits). BMI was included in the recursive partitioning models as a continuous variable, so that the trees could "split" at whichever cut point was most predictive of individuals' outcomes. The random forests technique can be used as an adjunct to the regression trees. This method combines values from a number (usually 100 or more) of hypothetical trees to estimate the overall relative importance of each variable in determining the outcome of interest. We used both methods in order to explore the overall and breast cancer mortality data and determine what patterns emerged.

Regression trees from analyses of overall and breast cancer-specific mortality are shown below, along with output from the Random Forests command in R. Values in the nodes represent average relative probability of mortality at any given point for individuals included in the group depicted by that node.

The tree for overall mortality (Figure C2a) shows that the highest mortality was found among women with progesterone receptor (PR)-negative disease who were under age 34 (5.1 relative

likelihood of mortality, with the latter predictive factor likely related to aggressive tumor types among younger women) and the lowest was found among women who had PR positive disease, a low or unknown tumor grade, and were under age 88 (0.099). Among women with higher-grade, PR+ tumors and among women with PR- tumors who were between ages 34 and 80, BMI appeared to be an important predictive factor. The points at which splits related to BMI occurred were in some cases relatively similar to the conventional BMI cutoffs, but not exactly. Among women with PR+ tumors and higher tumor grade, splits according to BMI occurred at a BMI of 38 kg/m^2 (women with BMI < 38 kg/m^2 had lower overall mortality compared to women with BMI ≥ 38 kg/m^2), then at a BMI of 31 kg/m2 (women with a BMI ≥ 31 kg/m^2 but lower than 38 kg/m2 had the second-lowest mortality of any groups defined by the tree). Another split also occurred according to BMI, farther down the tree and this time among women living in California, Georgia, or North Carolina only. In this group, a split occurred at a BMI of 28 lg/m^2, showing a substantial difference in mortality between women with BMI < 28 kg/m^2 (0.11 relative likelihood of mortality) and women with BMI ≥ 28 kg/m^2 (1.3 relative likelihood of mortality). Both age cutoffs and BMI cutoffs that defined nodes in the regression tree occurred at higher values within the range of the variable in question.

In the "variable importance" summary produced by R when creating the regression trees, BMI was second only to age in relative importance within the model. However, when a random forests approach was used (see Table C4a), BMI was found to be substantially less important; other factors, including AJCC stage, comorbidity level, insurance status, tumor grade, ER status, and race or ethnicity preceded it on the list.

The recursive partitioning process for modeling breast cancer mortality produced a tree (Figure C2b) that, at the optimal number of nodes as determined by cross-validation, included

few predictor variables, none of which was BMI. Breast cancer mortality was found to be highest among women with Stage III, high- or unknown-grade tumors, and lowest among women with Stage I or II tumors and positive or unknown PR status. Random forests output (Table C4b) confirmed that AJCC stage and tumor grade were the major contributors in explaining variation in breast cancer mortality.

In findings from our main Aim 1 analyses (Chapter 4), it was observed that BMI was associated with breast cancer only among women with Stage I disease. We therefore ran recursive partitioning analyses including only women with Stage I tumors. The resulting regression tree (Figure C2c) somewhat resembled the regression tree describing overall mortality, with age and BMI both being variables defining multiple splits.

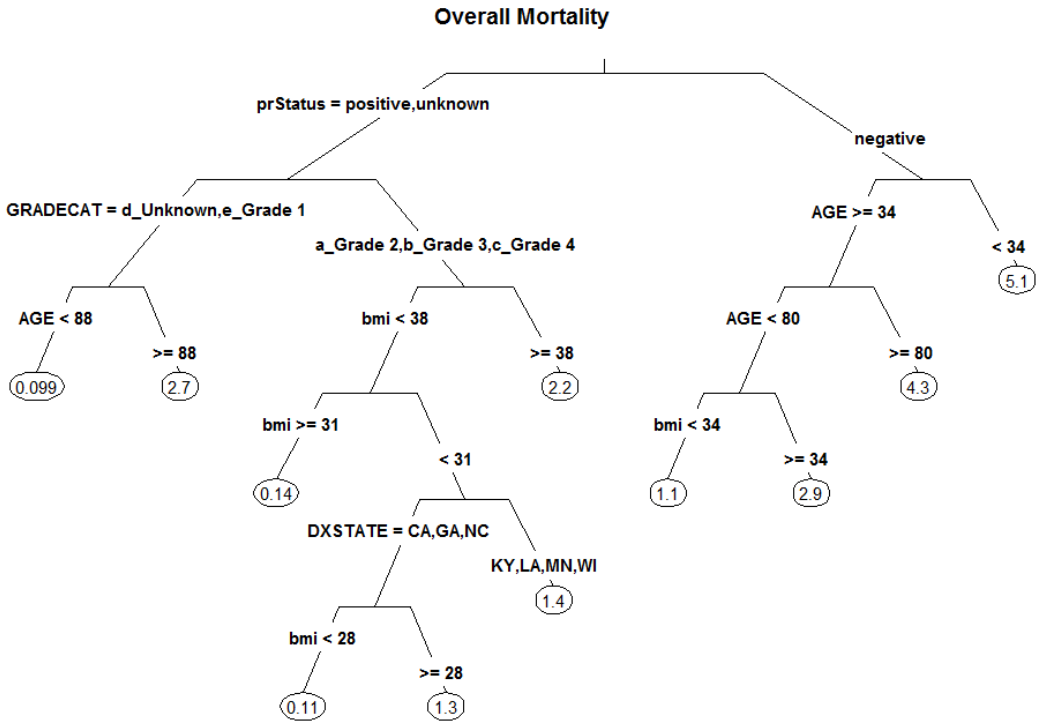

Figure C2a. Regression tree characterizing overall mortality according to BMI and other demographic characteristics included in the recursive partitioning analysis.

	Importance	Relative Imp
AGE	0.0457	1.0000
DERSTAGE_3	0.0389	0.8516
cclevel	0.0130	0.2842
INSURANCE	0.0083	0.1816
GRADECAT	0.0061	0.1326
erStatus	0.0035	0.0771
RACE_ETH	0.0032	0.0707
bmi	0.0017	0.0362
POVERTY	0.0011	0.0240
DXSTATE	0.0011	0.0236
erprY	0.0009	0.0202
prStatus	0.0003	0.0069
EDUCA	0.0001	0.0015
URBRURCAT	-0.0009	-0.0205

Table C4a. Random forests output for overall mortality recursive partitioning model, showing relative importance of variables in the model.

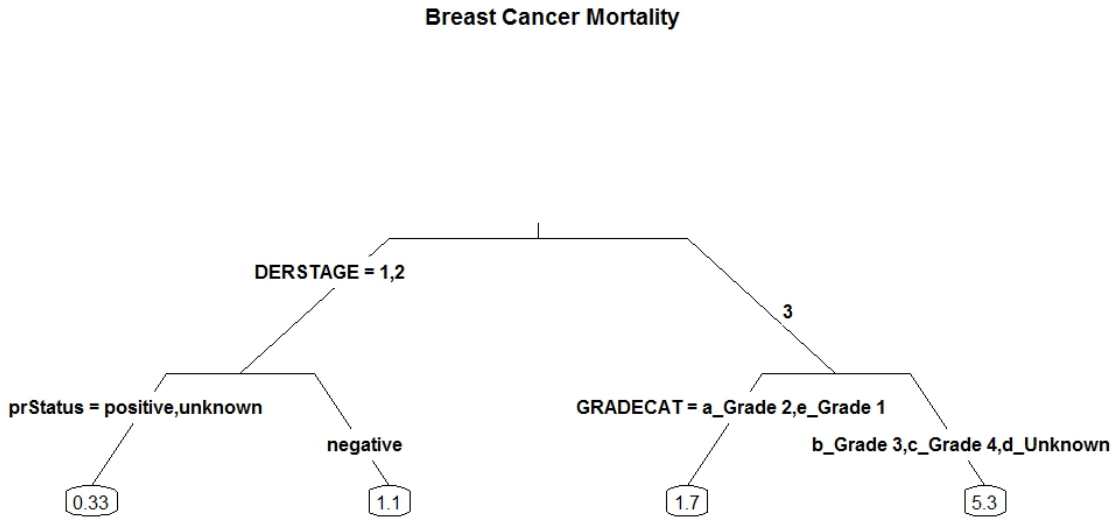

Figure C2b. Regression tree characterizing breast cancer mortality according to BMI and other demographic characteristics included in the recursive partitioning analysis.

	Importance	Relative Imp
DERSTAGE_3	0.0720	1.0000
GRADECAT	0.0223	0.3092
erStatus	0.0069	0.0961
AGE	0.0058	0.0808
INSURANCE	0.0051	0.0714
RACE_ETH	0.0043	0.0597
prStatus	0.0041	0.0567
erprY	0.0039	0.0538
cclevel	0.0022	0.0300
DXSTATE	0.0015	0.0207
POVERTY	0.0005	0.0064
EDUCA	0.0001	0.0019
bmi	-0.0007	-0.0099
URBRURCAT	-0.0020	-0.0274

Table C4b. Random forests output for breast cancer mortality recursive partitioning model, showing relative importance of variables in the model.

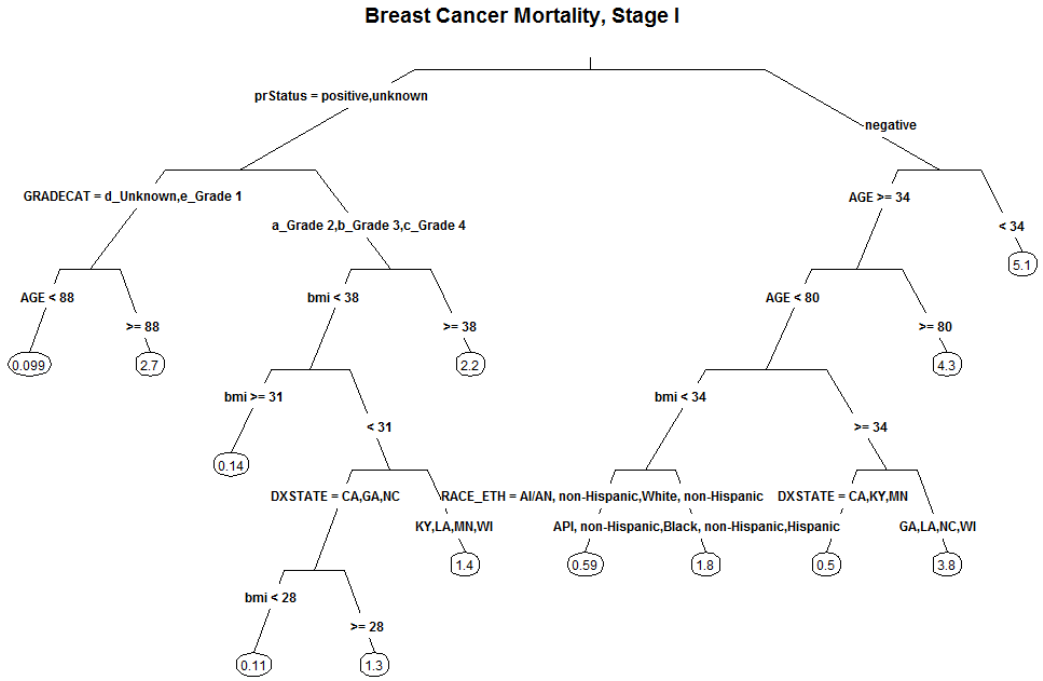

Figure C2c. Regression tree characterizing breast cancer mortality among women with Stage I disease according to BMI and other demographic characteristics included in the recursive partitioning analysis.

Models Using Vital Status Censored at 5 Years

In the POC-BP study, some women were followed longer than others due to the fact that not all tumor registries collected data on vital status for longer than the protocol-specified 5-year period; thus, the time of vital status collection ranged from 5 years to 11 years. Vital status data beyond 8 years past the time of diagnosis (2012) was available for a very small number of women (fewer than 10), so in our main analyses (Aim 1 and Aim 3), all observations were censored at 8 years in survival analyses to avoid any undue influence. We considered that this difference in the amount of person-time contributed by women according to the tumor registry through which they were identified was unlikely to bias our results because tumor registry is accounted for in the model design. However, as a means of confirming that this was unlikely to be an issue, we conducted sensitivity analyses in which all women's vital status was censored at 5 years; results were almost identical to those including all available follow-up time (Table C5).

Table C5. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for All-Cause Mortality and Breast Cancer-Specific Mortality According to Body Mass Index, With All Follow-up Times Censored at 5 Years

Patient Characteristic	All-Cause Mortality			Breast Cancer-Specific Mortality		
	HR	95% CI	p-value for trend	HR	95% CI	p-value for trend
Model Adjusting for Age, Tumor Stage, and Other Clinical and Demographic Characteristics[1]						
Body Mass Index (kg/m^2)						
< 18.5	1.31	0.80 - 2.15		**0.33**	0.12 - 0.93	
18.5-24.9	1 (ref)			1 (ref)		
25-29.9	0.82	0.67 - 1.01		0.87	0.64 - 1.19	
30-34.9	**0.75**	0.59 - 0.95		0.94	0.68 - 1.30	
≥35	0.85	0.67 - 1.08		0.93	0.64 - 1.35	
per 5 kg/m2 Δ	**0.93** (0.87 - 0.98)		**0.03**	0.98 (0.90 - 1.07)		0.65
Age at Diagnosis (years)	1.04	1.03 - 1.05	< 0.001	1.00	0.99 - 1.01	0.81
Tumor Stage (AJCC)						
I	1 (ref)			1 (ref)		
II	1.61	1.33 - 1.94	< 0.001	3.36	2.32 - 4.85	
III	3.92	3.18 - 4.84		12.21	8.56 - 17.44	< 0.001

Abbreviations: AJCC, American Joint Commission on Cancer

1. Model adjusted for age, tumor stage, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status, and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity.

APPENDIX D: Aim 2 Extra Tables, Sensitivity Analyses and Subgroup Analyses

This Appendix covers the following analyses:

Aim 2 Additional Tables (supplement to Paper 2)
Sensitivity Analyses Using Alternative Definitions of Guideline-Concordant Adjuvant Chemotherapy
Recursive Partitioning Approach (Classification Trees)

Additional Tables (referenced in Paper 2):

Tables D1, D2, and D3 present results from analyses focusing on associations between BMI and receipt or non-receipt of guideline-concordant treatments within specific domains, stratified according to other variables to produce subgroup-specific odds ratios (OR) and 95% confidence intervals (CI). These results are discussed in Paper 2. Table D1 presents stratified results for separate models examining BMI and lymph node sampling according to age category (age 69 or under versus 70 or older); Table D2 presents results for AJCC stage-specific (I, II, or III) models examining receipt of guideline-concordant adjuvant chemotherapy; and Table D3 shows results from separate models examining receipt of guideline hormonal therapy according to tumor stage category (Stage I, II, or III with T3N1M0 stage versus Stage III, non-T3N1M0).

Table D1. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Receipt of Guideline-Concordant Treatment (Lymph Node Sampling) Among Women With Stage I-III Breast Cancer, According to BMI Category, Stratified by Age

Treatment	Overall (N and %)	BMI				
		< 18.5	18.5-24.9	25 - 29.9	30 - 34.9	≥35
Lymph Nodes Sampled and Evaluated						
Age 69 or under						
Yes, N	4069 (97.9)	50	1202	1152	873	792
No, N	89 (2.1)	3	32	24	9	21
Odds Ratio (95% CI)[1]		0.31 (0.06 to 1.52)	1 (ref)	0.91 (0.48 to 1.74)	1.47 (0.57 to 3.82)	0.63 (0.31 to 1.28)
Age 70 and over						
Yes, N	1057 (88.2)	17	323	369	218	130
No, N	142 (11.8)	8	57	42	20	15
Odds Ratio (95% CI)[1]		0.80 (0.27 to 2.40)	1 (ref)	**2.50** (1.43 to 4.39)	**2.47** (1.22 to 5.02)	**2.25** (1.08 to 4.72)

Table D2. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Receipt of Guideline-Concordant Treatment (Adjuvant Chemotherapy) Among Women With Stage I-III Breast Cancer, According to Tumor Stage

Treatment	Overall (N and %)	BMI < 18.5	18.5-24.9	25 - 29.9	30 - 34.9	≥35	
Guideline-Concordant Adjuvant Chemotherapy							
Stage I							
Yes, N	2057 (84.1)	33	684	644	406	290	
No, N	390 (15.9)	8	108	119	78	77	
Odds Ratio (95% CI)[1]		0.77 (0.31 to 1.95)	1 (ref)	0.70 (0.47 to 1.05)	0.63 (0.38 - 1.03)	**0.51** (0.31 to 0.86)	p-trend
per 5 kg/m^2 Δ				**0.84** (0.75 to 0.95)			**0.01**
Stage II							
Yes, N	1696 (85.7)	24	494	475	361	342	
No, N	283 (14.3)	2	74	83	71	53	
Odds Ratio (95% CI)[1]		1.46 (0.31 to 6.98)	1 (ref)	0.74 (0.47 to 1.17)	0.88 (0.55 to 1.41)	1.42 (0.86 to 2.33)	
Stage III							
Yes, N	668 (85.0)	7	181	176	152	152	
No, N	118 (15.0)	3	29	40	24	22	
Odds Ratio (95% CI)[1]		0.25 (0.04 to 1.61)	1 (ref)	0.65 (0.32 to 1.34)	1.14 (0.44 to 2.98)	1.38 (0.57 to 3.36)	

Table D3. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Receipt of Guideline-Concordant Treatment (Hormonal Therapy) Among Women With Stage I-III Breast Cancer, According to BMI Category, Stratified by Tumor Stage Category

Treatment	Overall (N and %)	BMI < 18.5	18.5-24.9	25 - 29.9	30 - 34.9	≥35	
Guideline-Concordant Hormonal Therapy							
Stage I, II, and III (T3N1M0)							
Yes, N	3384 (79.0)	46	1015	1000	720	603	
No, N	899 (21.0)	14	293	266	173	153	
Odds Ratio (95% CI)[1]		1.19 (0.50 to 2.83)	1 (ref)	0.90 (0.71 to 1.15)	1.07 (0.81 to 1.41)	1.06 (0.75 to 1.51)	
Stage III (other than T3N1M0)							
Yes, N	578 (82.6)	7	151	146	136	138	
No, N	122 (17.4)	0	32	47	25	18	
Odds Ratio (95% CI)[1]		not estimable	1 (ref)	0.76 (0.40 to 1.47)	1.59 (0.77 to 3.26)	**2.58** (1.12 to 5.98)	p-trend
per 5 kg/m^2 Δ				**1.25** (1.05 - 1.48)			**0.01**

Sensitivity Analyses

Alternate Definitions of Guideline-Concordant Chemotherapy (and Overall Guideline Therapy)

As discussed in the second Paper (Chapter 5), the interpretation of results from analyses modeling receipt of guideline-concordant adjuvant chemotherapy, as well as those modeling receipt of overall guideline treatment, was somewhat complicated by the way that guideline-concordant chemotherapy receipt was defined. Among women under age 70 at the time of diagnosis, chemotherapy choice could be coded as either guideline-concordant, non-concordant, or unknown (in which case a woman would be excluded from analyses of guideline-concordant chemotherapy and guideline-concordant overall therapy); however, at age 70 an abrupt difference was seen, with all women over age 70 (n =1200) automatically being counted as having received guideline chemotherapy regardless of any other available information, or missing information, that might otherwise have put them in a different category. This same rule was applied to women with certain rare tumor histologies, as they too were not covered by the 2003 NCCN guidelines (although these women were less numerous; n = 434). This approach had a significant impact on the proportion of women counted as having recieved guideline-concordant chemotherapy and overall guideline-concordant therapy, and therefore – especially in light of the fact that age and BMI are so strongly associated – we decided to conduct sensitivity analyses comparing the approach just described with two others.

The first sensitivity analysis entailed simply excluding women who were over 70 and/or had the rare tumor histologies. Results from this analysis (Table D4) were somewhat similar to the results from the main analyses (Table 3 in Chapter 5; ORs and 95% CIs from this table provided within Table D4 for reference). As we found in the main analyses, BMI was not significantly

associated with odds of receiving guideline-concordant adjuvant chemotherapy. However, results from models using the alternate approach did show a borderline significant association suggesting that women with higher BMI were more likely to receive guideline chemotherapy ($p = 0.09$). Analyses stratified by stage did not, unlike the results from our main analyses, show that women with Stage I disease had lower likelihood of receiving guideline chemotherapy; rather, among these women a null association was observed (not shown). The findings regarding overall guideline-concordant therapy were very similar to those produced my the analyses in Chapter 5; results still showed that women with higher BMI were more likely to receive treatment concordant with guidelines in all the post-surgical treatment domains.

In the second sensitivity analysis, women not covered by guidelines due to their rare tumor characteristics were still automatically counted as having received guideline chemotherapy, but women over age 70 were not automatically treated as having received guideline treatment. Instead, these women were considered according to all characteristics except for age in determining what the guideline-concordant decision would be (an "age-blinded" approach). Results from this second sensitivity analysis are shown in Table D5. With regard to both guideline treatment in the adjuvant chemotherapy domain and overall guideline-concordant treatment, findings were very similar to those reported in Chapter 5.

Table D4. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Receipt of Guideline-Concordant (GC) Treatment Among Women With Stage I-III Breast Cancer, According to BMI Category - Alternate Approach to Defining GC Adjuvant Chemotherapy[1]

Treatment	Overall (N and %)	BMI					
		< 18.5	18.5-24.9	25 - 29.9	30 - 34.9	≥35	
Adjuvant Therapy							
Guideline-Concordant Adjuvant Chemotherapy[1]							
Yes, N	2657 (77.1)	26	817	734	559	521	
No, N	791 (22.9)	13	211	242	173	152	
Odds Ratio (95% CI)[2]		0.41 (0.15 to 1.19)	1 (ref)	0.80 (0.60 to 1.07)	0.99 (0.71 to 1.39)	1.27 (0.89 to 1.81)	
Original (Paper 2) Model Odds Ratios		0.74 (0.38-1.45)		0.68 (0.53-0.88)	0.75 (0.55-1.03)	0.91 (0.65-1.26)	
Overall Guideline-Concordant Therapy							
Yes, N	1188 (33.5)	7	359	321	257	244	
No, N	2355 (66.5)	39	701	703	478	434	p-trend
Odds Ratio (95% CI)[2]		**0.25** (0.10 to 0.63)	1 (ref)	0.83 (0.64 to 1.06)	1.24 (0.92 to 1.67)	1.13 (0.83 to 1.52)	
per 5 kg/m^2 Δ				**1.10** (1.02 - 1.18)			**0.01**
Original (Paper 2) Model Odds Ratios		0.55 (0.29 to 1.04)		0.87 (0.72 to 1.06)	1.11 (0.88 to 1.40)	1.14 (0.89 to 1.47)	
per 5 kg/m^2 Δ				1.09 (1.02 - 1.15)			0.01

1. As opposed to analyses presented in Paper 2, in this analysis women were excluded if their age (N = 1200) or tumor characteristics (N = 434) meant that NCCN guidelines did not make recommendations regarding adjuvant chemotherapy, rather than being treated automatically as having received guildeline therapy.

2. Model adjusted for age, tumor size, insurance type, poverty in census tract of residence, education levels in census tract of residence, urban/rural area, tumor grade, comorbidity level, and hormone receptor status. Survey sampling was stratified by tumor registry and by race/ethnicity.

Table D5. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Receipt of Guideline-Concordant (GC) Treatment Among Women With Stage I-III Breast Cancer, According to BMI Category - Alternate Approach to Defining GC Adjuvant Chemotherapy (Age-Blinded)[1]

Treatment	Overall (N and %)	BMI					
		< 18.5	18.5-24.9	25 - 29.9	30 - 34.9	≥35	
Guideline-Concordant Adjuvant Chemotherapy[1]							
Yes, N	3891 (75.1)	54	1186	1114	815	722	
No, N	1290 (24.9)	22	377	412	270	209	
Odds Ratio (95% CI)[2]		0.94 (0.45 to 1.97)	1 (ref)	**0.74** (0.59 to 0.94)	0.92 (0.71 to 1.20)	1.14 (0.85 to 1.52)	
Original (Paper 2) Model Odds Ratios		0.74 (0.38-1.45)		0.68 (0.53-0.88)	0.75 (0.55-1.03)	0.91 (0.65-1.26)	
Overall Guideline-Concordant Therapy							
Yes, N	1634 (37.4)	15	489	451	351	328	
No, N	2740 (63.6)	42	823	836	554	485	
Odds Ratio (95% CI)[2]		0.66 (0.33 to 1.30)	1 (ref)	0.83 (0.67 to 1.02)	1.17 (0.92 to 1.48)	1.15 (0.89 to 1.48)	p-trend
per 5 kg/m^2 Δ				**1.08** (1.01 to 1.15)			**0.01**
Original (Paper 2) Model Odds Ratios		0.55 (0.29 to 1.04)	1 (ref)	0.87 (0.72 to 1.06)	1.11 (0.88 to 1.40)	1.14 (0.89 to 1.47)	
per 5 kg/m^2 Δ				1.09 (1.02 - 1.15)			0.01

1. As opposed to analyses presented in Paper 2, in this analysis (the "age-blinded chemotherapy" approach) women were automatically treated as having received guideline therapy if their tumor characteristics (rare histologies) meant that NCCN guidelines did not make recommendations regarding adjuvant chemotherapy (N = 434); however, women over 70 (N = 1200) were not automatically treated as having received guildeline treatment, but instead considered according to all characteristics except for age in determining what the guideline-concordant decision would be.

2. Model adjusted for age, tumor size, insurance type, poverty in census tract of residence, education levels in census tract of residence, urban/rural area, tumor grade, comorbidity level, and hormone receptor status. Survey sampling was stratified by tumor registry and by race/ethnicity.

Recursive Partitioning Approach (Classification Trees)

We conducted recursive partitioning analyses, similar to those described in Appendix C for overall and breast cancer-specific mortality, using R to produce classification trees identifying characteristics that were important in determining likelihood of receiving guideline-concordant treatments. As in the models described in Appendix C, BMI was included as a continuous variable so that splits could occur at the cutpoint, or cutpoints, that provided the most homogeneous groupings of individuals in terms of likelihood of the outcome of interest. The random forests technique was again used as adjunct to the classification trees.

Classification trees resulting from recursive partitioning analyses modeling likelihood of overall guideline-concordant treatment as well as guideline therapies within specific treatment domains are shown below, along with output from the Random Forests command in R. Values in the nodes represent average probability of receipt of guideline treatment for individuals included in the group depicted by that node. The classification tree for overall guideline-concordant treatment (Figure D1a) did not indicate that BMI was an important contributor to determining likelihood of guideline treatment when compared to geographic area, tumor size, lymph node status, and age. However, an examination of the output from the recursive partitioning process showed that when splits were decided, alternative splits were possible that offered a very similar amount of improvement in the model; this indicates a lack of stability in the model and suggests a random forests approach will provide a better chance of allowing the true patterns to emerge. In the random forests output (Table D6a), age and BMI emerge as important predictors of overall guideline-concordant treatment receipt.

Figures D1b-D1e and Tables D6c-D6e show the results of recursive partitioning analyses modeling receipt of guideline therapies within specific treatment domains: radiation therapy,

adjuvant chemotherapy, adjuvant chemotherapy with the "age-blinded" definition of guideline concordance, and hormonal therapy. In general, BMI was not the basis of splits within the trees resulting from these models once the trees were trimmed to the optimal number of splits; however, in several cases the random forests approach showed that BMI was an important variable in determining likelihood of guideline treatment within a specific domain. Variables that tended to supersede BMI (in importance in results from both approaches) included geographic region (DXSTATE, the tumor registry through which a woman was identified), age at diagnosis, and tumor characteristics (size and grade).

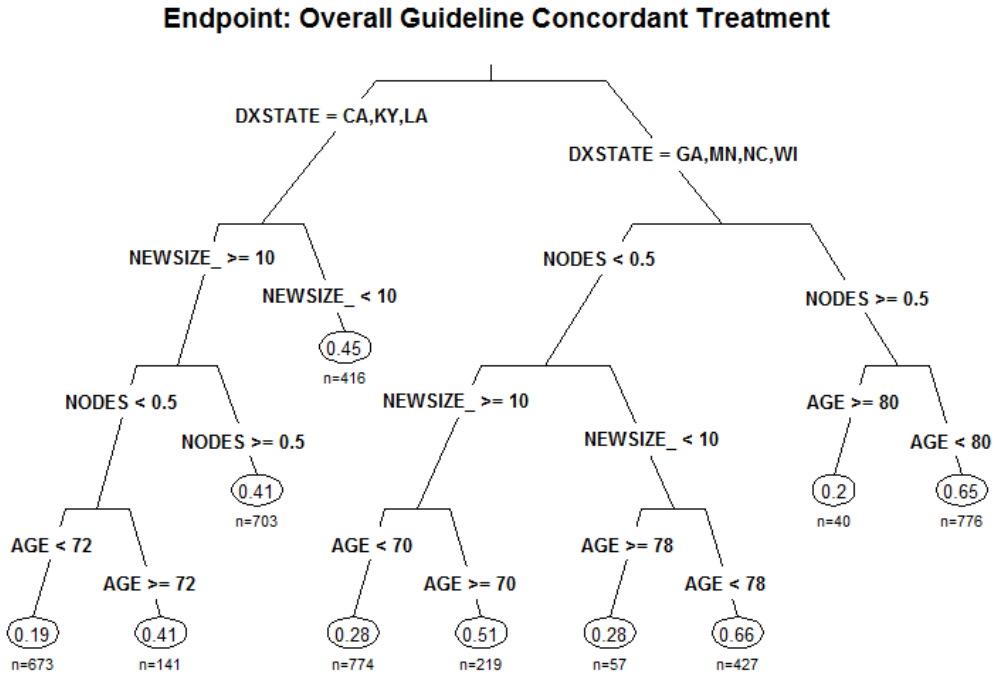

Figure D1a. Classification tree characterizing likelihood of receiving overall guideline-concordant treatment.

```
Node number 1: 4226 observations,    complexity param=0.02300092
  mean=0.4256981, MSE=0.2444792
  left son=2 (1933 obs) right son=3 (2293 obs)
  Primary splits:
      DXSTATE    splits as  LRLLRRR,      improve=0.023000920, (0 missing)
      NODES      < 0.5      to the left,  improve=0.020097160, (201 missing)
      NEWSIZE_RT < 10.5     to the right, improve=0.018352780, (38 missing)
      EDUCA      splits as  RRL,         improve=0.009138250, (0 missing)
      AGE        < 81.5     to the right, improve=0.008315884, (0 missing)
  Surrogate splits:
      URBRURCAT splits as  LLRR,    agree=0.629, adj=0.189, (0 split)
      POVERTY   splits as  RLR,     agree=0.615, adj=0.159, (0 split)
      RACECAT   splits as  LRLRLR,  agree=0.615, adj=0.158, (0 split)
      EDUCA     splits as  RRL,     agree=0.595, adj=0.114, (0 split)
      INSURANCE splits as  LRRRR,   agree=0.559, adj=0.037, (0 split)

Node number 2: 1933 observations,    complexity param=0.009085947
  mean=0.3440248, MSE=0.2256717
  left son=4 (1517 obs) right son=5 (416 obs)
  Primary splits:
      NEWSIZE_RT < 10.5     to the right, improve=0.013523960, (17 missing)
      NODES      < 0.5      to the left,  improve=0.011121390, (110 missing)
      INSURANCE  splits as  LRLRR,        improve=0.008193078, (0 missing)
      RACECAT    splits as  RRLLRR,       improve=0.005551360, (0 missing)
      erStat     < 0.5      to the right, improve=0.004745040, (69 missing)
```

IncNodePurity	
bmi	144.37156
AGE	139.71210
cclevel	32.32997
EDUCA	15.58931
POVERTY	13.18941
URBRURCAT	35.87825
NEWSIZE_RT	144.57121
GRADECAT	49.24949
NODES	39.77105
erStat	15.73380
prStat	17.83260
INSURANCE	41.12849
RACECAT	38.32399
DXSTATE	80.26892

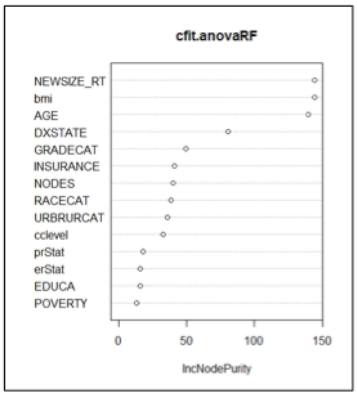

Table D6a. Recursive partitioning output (at top) showing improvements to overall guideline concordant treatment model offered by primary split and alternate primary splits for two different nodes; Random forests output for overall guideline-concordant treatment recursive partitioning model, showing relative importance of variables in the model.

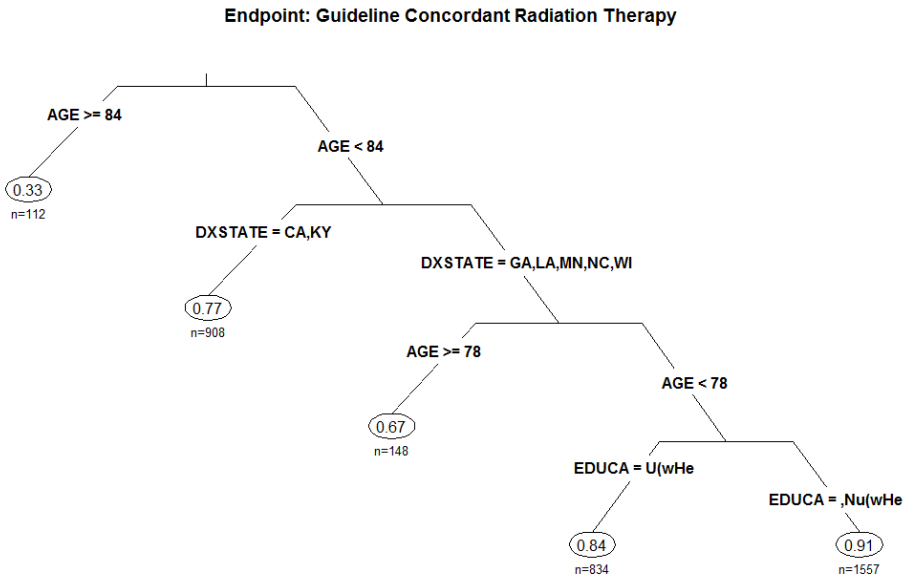

Figure D1b. Classification tree characterizing likelihood of receiving guideline-concordant radiation therapy.

```
Variable importance
      AGE   DXSTATE     EDUCA   RACECAT   POVERTY INSURANCE
       70        16         6         4         3         1

Node number 1: 3559 observations,    complexity param=0.05707256
  mean=0.8291655, MSE=0.1416501
  left son=2 (112 obs) right son=3 (3447 obs)
  Primary splits:
      AGE       < 83.5 to the right, improve=0.057072560, (0 missing)
      DXSTATE   splits as  LRLRRRR,  improve=0.015963780, (0 missing)
      INSURANCE splits as  LLRRR,    improve=0.012835350, (0 missing)
      POVERTY   splits as  LLR,      improve=0.009023025, (0 missing)
      cclevel   < 1.5  to the right, improve=0.008907875, (0 missing)

Node number 2: 112 observations
  mean=0.3303571, MSE=0.2212213

Node number 3: 3447 observations,    complexity param=0.01563159
  mean=0.8453728, MSE=0.1307176
  left son=6 (908 obs) right son=7 (2539 obs)
  Primary splits:
      DXSTATE   splits as  LRLRRRR,  improve=0.017489300, (0 missing)
      AGE       < 77.5 to the right, improve=0.015535090, (0 missing)
      POVERTY   splits as  LLR,      improve=0.009291366, (0 missing)
      INSURANCE splits as  LLLRR,    improve=0.008579957, (0 missing)
      EDUCA     splits as  LRL,      improve=0.008372434, (0 missing)
  Surrogate splits:
      RACECAT splits as  LRLRLR,   agree=0.803, adj=0.251, (0 split)
      AGE     < 24.5 to the left,  agree=0.739, adj=0.008, (0 split)
      bmi     < 14.5 to the left,  agree=0.738, adj=0.007, (0 split)
```

Table D6b. Random forests approach was not used for guideline-concordant radiation therapy recursive partitioning model; the output above is from the showing relative importance of variables in the model after trimming to the number of splits (5) found to be optimal in the cross-validation step.

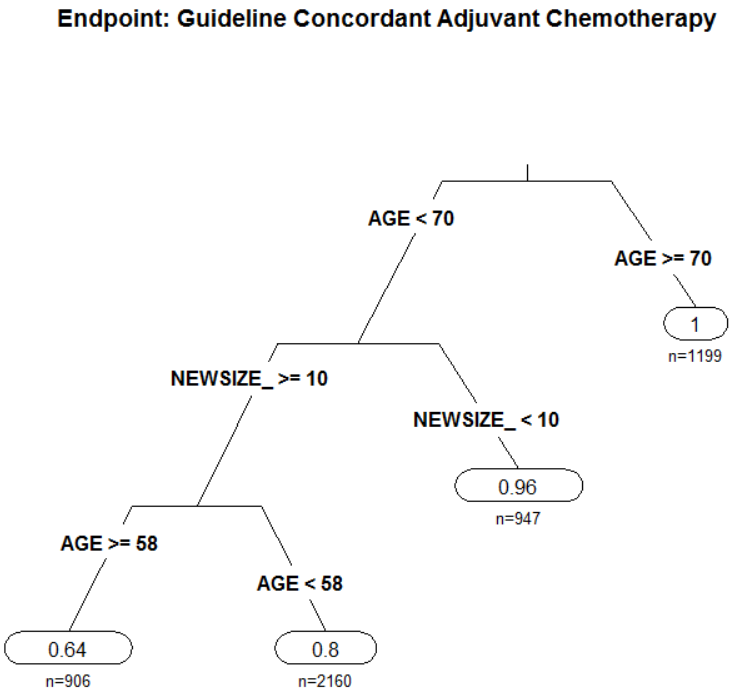

Figure D1c. Regression tree characterizing likelihood of receiving guideline-concordant adjuvant chemotherapy (original model definition).

	IncNodePurity
bmi	95.006894
AGE	116.265982
cclevel	19.284365
EDUCA	10.729114
POVERTY	9.251861
URBRURCAT	19.407876
NEWSIZE_RT	102.253196
GRADECAT	29.125838
erStat	10.027805
prStat	11.233205
INSURANCE	22.107138
RACECAT	24.736092
DXSTATE	43.734578

Table D6c. Random forests output for guideline-concordant adjuvant chemotherapy (original definition) recursive partitioning model, showing relative importance of variables in the model.

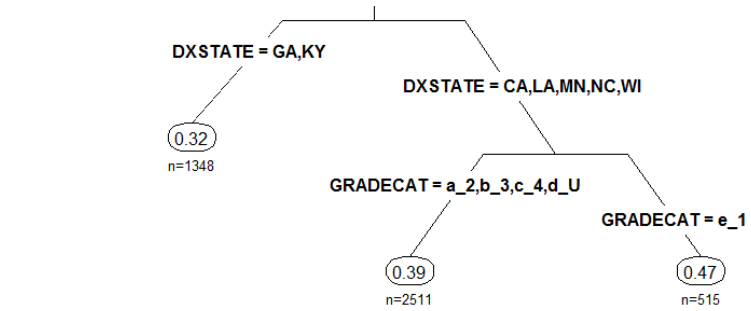

Figure D1d. Regression tree characterizing likelihood of receiving guideline-concordant adjuvant chemotherapy (age-blinded definition).

	IncNodePurity
bmi	181.26943
AGE	146.50603
cclevel	37.08824
EDUCA	19.51647
POVERTY	17.26879
URBRURCAT	37.76553
NEWSIZE_RT	133.59478
GRADECAT	44.34975
erStat	15.29567
prStat	18.99914
INSURANCE	44.50253
RACECAT	41.11640
DXSTATE	68.54578

Table D6d. Random forests output for guideline-concordant adjuvant chemotherapy (age-blinded definition) recursive partitioning model, showing relative importance of variables in the model.

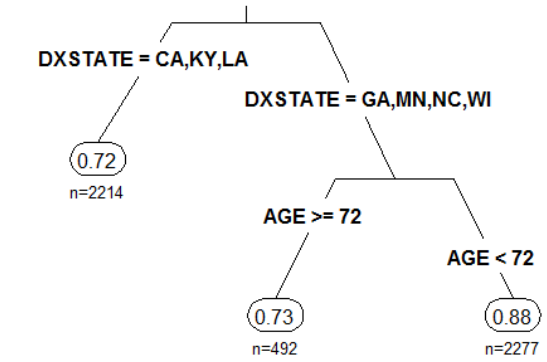

Figure D1e. Regression tree characterizing likelihood of receiving guideline-concordant hormonal therapy.

	IncNodePurity
bmi	95.006894
AGE	116.265982
cclevel	19.284365
EDUCA	10.729114
POVERTY	9.251861
URBRURCAT	19.407876
NEWSIZE_RT	102.253196
GRADECAT	29.125838
erStat	10.027805
prStat	11.233205
INSURANCE	22.107138
RACECAT	24.736092
DXSTATE	43.734578

Table D6e. Random forests output for guideline-concordant hormonal therapy recursive partitioning model, showing relative importance of variables in the model.

APPENDIX E: Aim 3 Sensitivity Analyses and Subgroup Analyses

The National Comprehensive Cancer Network (NCCN) guidelines are updated regularly, every one to two years. Therefore, findings from analyses addressing our third Aim might not be generalizable, in the sense that knowing whether receipt or nonreceipt of treatment that adhered to NCCN guidelines available in 2004 (v1.2003) predicted mortality, or mediated the relationship between obesity and mortality, would not answer the question of whether treatment adherent to guidelines available today had the same impact. A sensitivity analysis was conducted to investigate whether our findings would be different if the 2014 NCCN guidelines were used to define women's treatment as guideline-concordant or non-concordant (although naturally, the 2014 guidelines were not available when the women were diagnosed in 2004).

We re-ran the analyses from Aim 3 using new variables representing guideline-concordant treatment in the domains of radiation therapy, adjuvant chemotherapy, and hormonal therapy. Guidelines for radiation therapy did not change substantially for women with Stage I-III disease between the 2003 and 2014 versions. However, the treatment pathways for adjuvant systemic therapies in the 2014 guidelines are structured differently from the 2003 guidelines, reflecting an increased understanding of the importance of Her2-neu receptor status (in addition to ER and PR status) in decision-making regarding adjuvant therapies. In the 2014 guidelines, women are characterized as being in one of five different groups defined according to Her2-neu receptor and ER/PR receptor status (Her2+,ER/PR+; Her2+,ER/PR-, Her2-,ER/PR+, Her2-,ER/PR-) *or* the presence of "favorable tumor characteristics" (such as tubular histology); separate treatment pathways are then given for each of these groups, which include recommendations for adjuvant chemotherapy as well as hormonal therapy. Therefore, we created a single variable for "guideline-concordant adjuvant systemic therapy." It should be noted that because Her2-neu

status and/or ER/PR status was unknown for 843 women (16%) in the original Aim 3 analytic data set, these women had to be excluded from analyses involving guideline-concordant systemic therapy and those involving overall guideline-concordant treatment. In addition to the changes related to Her2-neu status, the most significant change affecting our analyses was the fact that the 2014 guidelines recommended trastuzumab (Herceptin) as an accompaniment to adjuvant chemotherapy in all situations where adjuvant chemotherapy was recommended. For roughly 2% of women, it was unknown whether trastuzumab was received, but having missing information on trastuzumab meant we could not determine guideline-concordance of systemic treatment in only 0.8%. Trastuzumab was prescribed very infrequently to the women diagnosed in 2004, with only about 3% receiving this monoclonal antibody as part of their treatment.

Table E1 shows results from the logistic regression models for receipt of guideline-concordant therapies according to BMI. Overall, as defined according to the 2014 guidelines, 79% of women received radiation therapy that was guideline-concordant. Higher BMI was associated with higher odds of receiving radiation therapy in line with the 2014 guidelines (OR for BMI $\geq$ 35 kg/m^2 versus 18.5-24.9 kg/m^2 = 1.31, 95% CI, 1.04-1.65; OR for 5 kg/m^2 greater BMI = 1.07, 95% CI, 1.01-1.13, p = 0.03). Only 29% of women received systemic therapy that was guideline-concordant. A substantial proportion of this can be attributed to the very low usage of trastuzumab; 28% of women characterized as not having received guideline systemic therapy would have been counted as having received it if trastuzumab had been a part of their treatment. Higher BMI was associated with lower odds of receiving systemic therapy in line with the 2014 guidelines (OR for 5 kg/m^2 greater BMI = 0.94, 95% CI, 0.88-1.00; p = 0.04), although the pattern of odds ratios for the BMI categories indicates this may have been true only for women in the highest part of the BMI range. In all, 24% of women were found to have received overall

guideline-concordant therapy (in comparison to 43% in our Aim 3 analysis results). Higher BMI was associated with higher odds of receiving overall guideline-concordant treatment (OR for 5 kg/m^2 difference in BMI = 1.09, 95% CI 1.02-1.17, p = 0.02); this was in line with the findings from our Aim 3 analyses, in which the OR for a 5 kg/m^2 difference in BMI was 1.08.

Table E1. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Receipt of Guideline-Concordant Treatment, As Defined by 2014 NCCN Guidelines, Among Women With Stage I-III Breast Cancer, According to BMI Category

Treatment	Overall (N and %)	BMI					
		< 18.5	18.5-24.9	25 - 29.9	30 - 34.9	≥35	p-trend
Guideline-Concordant Radiation Therapy							
Yes, N	2311 (79%)	23	653	705	483	447	
No, N	604 (21%)	15	180	180	114	115	
Odds Ratio (95% CI)[1]		0.57 (0.26 - 1.27)	1 (ref)	1.08 (0.89 - 1.31)	0.96 (0.75 - 1.22)	**1.31** (1.04 - 1.65)	
per 5 kg/m2 Δ BMI				**1.07** (1.01 - 1.13)			**0.03**
Guideline-Concordant Adjuvant Systemic Therapy[2]							
Yes, N	1115 (29%)	15	331	316	229	224	
No, N	2690 (71%)	44	787	837	554	468	
Odds Ratio (95% CI)[1]		1.46 (0.70 - 3.02)	1 (ref)	1.19 (0.96 - 1.46)	1.15 (0.91 - 1.45)	0.82 (0.64 - 1.06)	
per 5 kg/m2 Δ BMI				**0.94** (0.88 - 1.00)			**0.04**
Overall Guideline-Concordant Therapy							
Yes, N	946 (24%)	10	280	265	200	191	
No, N	2916 (76%)	51	855	903	593	514	
Odds Ratio (95% CI)[1]		0.48 (0.21 - 1.08)	1 (ref)	0.84 (0.67 - 1.07)	1.00 (0.79 - 1.27)	1.20 (0.91 - 1.59)	
per 5 kg/m2 Δ BMI				**1.09** (1.02 - 1.17)			**0.02**

1. Model adjusted for age, tumor size, insurance type, poverty in census tract of residence, education levels in census tract of residence, urban/rural area, tumor grade, comorbidity level, and hormone receptor status. Survey sampling was stratified by tumor registry and by race/ethnicity.

2. Guideline Adjuvant Systemic Therapy defined as guideline-concordant adjuvant chemotherapy (including trastuzumab) and guideline-concordant hormonal therapy.

Next, we re-ran the analyses from Aim 3 in which receipt of overall guideline-concordant treatment was tested as a potential mediator of the relationship between BMI and mortality. Table E2 shows results of these analyses, with hazards ratios for all-cause mortality or breast cancer mortality according to BMI without (Model 1) and with (Model 2) inclusion of the variable indicating receipt of treatment in line with the 2014 guidelines. Again, the results were for the most part similar to those found in our Aim 3 analyses (see Table 3 in Chapter 6): in the group as a whole, higher BMI was not associated with breast cancer-specific mortality, and was associated with lower hazard for overall mortality (HR for 5 kg/m^2 higher BMI = 0.93, 95% CI 0.86-0.99; p = 0.03), and the addition of the guideline-concordance indicator variable to the model had little to no impact on hazard ratio point estimates for overall or breast cancer mortality. Guideline-concordant treatment was, as in the results shown in Table 3 of Chapter 6, independently associated with lower hazard for overall mortality (HR = 0.78, 95% CI 0.62-0.98, p = 0.03); however, it was not found to be significantly associated with breast cancer mortality.

Table E2. Hazard Ratios (HR) and 95% Confidence Intervals (CI) for All-Cause Mortality and Breast Cancer-Specific Mortality According to Body Mass Index, Not Accounting (Model 1) and Accounting (Model 2) for Guideline-Concordant Treatment Defined According to 2014 Guidelines

	All-Cause Mortality			**Breast Cancer-Specific Mortality**		
	HR	95% CI	p-value	HR	95% CI	p-value
Model 1: Adjusting for Age, Tumor Stage, and Other Clinical and Demographic Characteristics[1]						
Body Mass Index (kg/m^2)						
< 18.5	1.03	0.56 - 1.90		0.35	0.12 - 1.01	
18.5-24.9	1 (ref)			1 (ref)		
25-29.9	**0.78**	0.61 - 0.99		0.77	0.54 - 1.08	
30-34.9	0.77	0.59 - 1.00		0.87	0.61 - 1.25	
≥35	0.82	0.62 - 1.08		0.79	0.52 - 1.20	
per 5 kg/m2 BMI Δ	**0.92**	0.86 - 0.99	**0.03**	0.94	0.85 - 1.03	0.20
Model 2: Adjusting for Age, Tumor Stage, and Other Characteristics, and for Receipt or Nonreceipt of Guideline-Concordant Treatment[2]						
Body Mass Index (kg/m^2)						
< 18.5	0.99	0.54 - 1.84		0.35	0.12 - 1.00	
18.5-24.9	1 (ref)			1 (ref)		
25-29.9	**0.77**	0.61 - 0.98		0.77	0.54 - 1.08	
30-34.9	**0.77**	0.59 - 1.00		0.87	0.61 - 1.25	
≥35	0.82	0.62 - 1.08		0.79	0.52 - 1.20	
per 5 kg/m^2 Δ	**0.93**	0.86 - 0.99	**0.03**	0.94	0.85 - 1.04	0.21
Guideline-Concordant Treatment Received	**0.78**	0.62 - 0.98	**0.03**	0.98	0.72 - 1.34	0.92

1. Model 1 adjusted for age, tumor stage, insurance type, poverty in census tract of residence, education levels in census tract of residence, urbanicity of residence area, tumor grade, hormone receptor status (estrogen receptor and progesterone receptor), and comorbidity level. Survey sampling was stratified by tumor registry and by race/ethnicity.

2. Model 2 adjusted for the same variables as Model 1, with the addition of a variable indicating receipt of guideline-concordant treatment. Guideline-concordant treatment was defined as treatment following 2014 National Comprehensive Cancer Network (NCCN) recommendations for radiation therapy, adjuvant chemotherapy, adjuvant chemotherapy regimen, and hormonal therapy.

APPENDIX F: Tables Showing Hazard Ratios or Odds Ratios for All Covariates

Aim 1 Hazards Ratios (Shown in Table 3 of Chapter 4)

Table F1a. Overall Mortality Model. Hazard Ratios (OR) and 95% Confidence Intervals (CI) for All-Cause Mortality for All Covariates

Stage I, II, and III Breast Cancer Patients from the POC-BP Study (2004)

Effect	HR	95% Wald Confidence Limits		p-value[1]
BMI < 18.5 versus 18.5-24.9	1.31	0.80	2.15	0.29
BMI 18.5-24.9	1.00	.	.	.
BMI 25.0-29.9 versus 18.5-24.9	0.82	0.67	1.01	0.06
BMI 30.0-34.9 versus 18.5-24.9	**0.75**	0.59	0.95	0.02
BMI ≥ 35 versus 18.5-24.9	0.85	0.67	1.08	0.18
Age (years)	**1.04**	1.03	1.05	<.0001
Tumor Stage (III versus I, AJCC staging criteria)	**3.92**	3.18	4.84	<.0001
Tumor Stage (II versus I, AJCC staging criteria)	**1.61**	1.33	1.94	<.0001
Tumor Stage I	1.00	.	.	.
Comorbidity level (0-3)	**1.40**	1.25	1.56	<.0001
Tumor grade (2 versus 1)	1.10	0.85	1.42	0.46
Tumor grade (3 versus 1)	**1.94**	1.51	2.50	<.0001
Tumor grade (4 versus 1)	1.52	0.73	3.17	0.26
Tumor grade (unknown versus 1)	1.21	0.82	1.80	0.34
Tumor grade 1	1.00	.	.	.
ER Status (positive, negative, or unknown)	0.91	0.73	1.13	0.37
PR Status (positive, negative, or unknown)	0.92	0.75	1.12	0.40
Insurance: Medicaid versus private	1.10	0.67	1.79	0.72
Insurance: Medicare only versus private	0.88	0.55	1.41	0.60
Insurance: none versus private	1.34	0.74	2.42	0.34
Insurance: unknown versus private	0.70	0.44	1.11	0.13
Insurance: private	1.00	.	.	.
Education (lower versus higher, census tract level)	1.13	0.91	1.39	0.275
Poverty (higher vs. lower, census tract level)	0.91	0.72	1.15	0.44
Urbanicity (100% urban versus 100% rural)	1.08	0.85	1.38	0.53
Urbanicity (mixed urban-rural versus 100% rural)	1.19	0.92	1.54	0.19
Urbanicity: 100% rural	1.00	.	.	.

1. p-value from analysis of maximum likelihood estimates.

Table F1b. Breast Cancer Mortality Model. Hazard Ratios (OR) and 95% Confidence Intervals (CI) for Breast Cancer-Specific Mortality for All Covariates

Stage I, II, and III Breast Cancer Patients from the POC-BP Study (2004)

Effect	HR	95% Wald Confidence Limits		p-value[1]
BMI < 18.5 versus 18.5-24.9	**0.33**	0.12	0.93	0.04
BMI 18.5-24.9	1.00	.	.	.
BMI 25.0-29.9 versus 18.5-24.9	0.87	0.64	1.19	0.38
BMI 30.0-34.9 versus 18.5-24.9	0.94	0.68	1.30	0.72
BMI ≥ 35 versus 18.5-24.9	0.93	0.64	1.35	0.70
Age (years)	1.00	0.99	1.01	0.81
Tumor Stage (III versus I, AJCC staging criteria)	**12.22**	8.56	17.44	<.0001
Tumor Stage (II versus I, AJCC staging criteria)	**3.36**	2.32	4.85	<.0001
Tumor Stage I	1.00	.	.	.
Comorbidity level (0-3)	1.04	0.87	1.26	0.66
Tumor grade (2 versus 1)	**2.26**	1.16	4.40	0.02
Tumor grade (3 versus 1)	**5.83**	3.06	11.13	<.0001
Tumor grade (4 versus 1)	**3.93**	1.25	12.40	0.02
Tumor grade (unknown versus 1)	**2.33**	1.01	5.35	0.05
Tumor grade 1	1.00	.	.	.
ER Status (positive, negative, or unknown)	0.89	0.65	1.22	0.46
PR Status (positive, negative, or unknown)	0.77	0.56	1.04	0.09
Insurance: Medicaid versus unknown	1.12	0.56	2.22	0.75
Insurance: Medicare only versus unknown	1.09	0.54	2.18	0.82
Insurance: none versus unknown	0.97	0.44	2.15	0.94
Insurance: private versus unknown	0.84	0.43	1.63	0.61
Insurance: unknown	1.00	.	.	.
Education (lower versus higher, census tract level)	1.00	0.73	1.39	0.98
Poverty (higher vs. lower, census tract level)	1.10	0.77	1.55	0.61
Urbanicity (100% urban versus 100% rural)	0.96	0.67	1.39	0.84
Urbanicity (mixed urban-rural versus 100% rural)	1.09	0.74	1.61	0.66
Urbanicity: 100% rural	1.00	.	.	.

1. p-value from analysis of maximum likelihood estimates.

Aim 2 Odds Ratios (Shown in Table 3 of Chapter 5)

Table F2a. Lymph Node Sampling and Evaluation Model. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Specific Treatment Receipt for All Covariates

Stage I, II, and III Breast Cancer Patients from the POC-BP Study (2004)

Effect	OR	95% Wald Confidence Limits	
BMI < 18.5 versus 18.5-24.9	0.75	0.27	2.07
BMI 25.0-29.9 versus 18.5-24.9	**1.86**	1.19	2.91
BMI 30.0-34.9 versus 18.5-24.9	**2.01**	1.16	3.48
BMI ≥ 35 versus 18.5-24.9	1.13	0.68	1.88
Age (years)	**0.92**	0.90	0.94
Comorbidity level (0-3)	1.01	0.79	1.30
Education (lower versus higher, census tract level)	1.32	0.83	2.10
Poverty (higher vs. lower, census tract level)	0.67	0.40	1.10
Urbanicity (100% urban versus 100% rural)	0.99	0.60	1.65
Urbanicity (mixed urban-rural versus 100% rural)	1.09	0.64	1.85
Insurance: Medicaid versus private	0.75	0.48	1.19
Insurance: Medicare only versus private	0.97	0.66	1.43
Insurance: none versus private	**0.21**	0.08	0.57
Insurance: unknown versus private	1.35	0.41	4.48
Tumor size: 0.51-1 cm versus 0.5 cm or less	**2.69**	1.53	4.73
Tumor size: 1.01-1.99 cm versus 0.5 cm or less	**3.75**	2.17	6.50
Tumor size: 2.0 - 4.9 cm versus 0.5 cm or less	**3.56**	2.06	6.16
Tumor size: 5 cm or greater versus 0.5 cm or less	**2.89**	1.31	6.38
Tumor grade (I-IV or unknown)	0.96	0.89	1.04
ER Status (positive, negative, or unknown)	0.88	0.58	1.35
PR Status (positive, negative, or unknown)	0.96	0.65	1.43

Table F2b. Guideline-Concordant Radiation Therapy Model. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Specific Treatment Receipt for All Covariates

Stage I, II, and III Breast Cancer Patients from the POC-BP Study (2004)

Effect	OR	95% Wald Confidence Limits	
BMI < 18.5 versus 18.5-24.9	**0.30**	0.12	0.74
BMI 18.5-24.9	1.00	.	.
BMI 25.0-29.9 versus 18.5-24.9	0.91	0.66	1.24
BMI 30.0-34.9 versus 18.5-24.9	0.95	0.64	1.42
BMI ≥ 35 versus 18.5-24.9	0.96	0.64	1.43
Age (years)	**0.96**	0.95	0.97
Comorbidity level (0-3)	0.91	0.76	1.09
Education (lower versus higher, census tract level)	0.99	0.71	1.39
Poverty (higher vs. lower, census tract level)	0.70	0.49	1.01
Urbanicity (100% urban versus 100% rural)	0.74	0.51	1.08
Urbanicity (mixed urban-rural versus 100% rural)	0.87	0.58	1.31
Insurance: Medicaid versus private	0.70	0.48	1.02
Insurance: Medicare only versus private	**1.45**	1.02	2.06
Insurance: none versus private	0.81	0.36	1.83
Insurance: unknown versus private	1.77	0.87	3.61
Tumor size: 0.51-1 cm versus 0.5 cm or less	**2.01**	1.19	3.41
Tumor size: 1.01-1.99 cm versus 0.5 cm or less	**1.76**	1.12	2.76
Tumor size: 2.0 - 4.9 cm versus 0.5 cm or less	1.20	0.75	1.92
Tumor size: 5 cm or greater versus 0.5 cm or less	1.21	0.66	2.23
Tumor size: Unknown versus 0.5 cm or less	**3.04**	1.22	7.59
Lymph node status (positive versus negative)	**0.66**	0.51	0.87
Tumor grade (I-IV or unknown)	0.97	0.90	1.04
ER Status (positive, negative, or unknown)	1.35	0.98	1.86
PR Status (positive, negative, or unknown)	1.23	0.91	1.65

Table F2c. Guideline-Concordant Adjuvant Chemotherapy Model. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Specific Treatment Receipt for All Covariates

Stage I, II, and III Breast Cancer Patients from the POC-BP Study (2004)

Effect	OR	95% Wald Confidence Limits	
BMI < 18.5 versus 18.5-24.9	0.74	0.38	1.45
BMI 25.0-29.9 versus 18.5-24.9	**0.68**	0.53	0.88
BMI 30.0-34.9 versus 18.5-24.9	0.75	0.55	1.03
BMI ≥ 35 versus 18.5-24.9	0.91	0.65	1.26
Age (years)	**1.02**	1.01	1.03
Comorbidity level (0-3)	1.07	0.92	1.24
Education (lower versus higher, census tract level)	0.83	0.64	1.09
Poverty (higher vs. lower, census tract level)	0.80	0.58	1.10
Urbanicity (100% urban versus 100% rural)	1.00	0.75	1.35
Urbanicity (mixed urban-rural versus 100% rural)	**1.45**	1.04	2.02
Insurance: Medicaid versus private	0.88	0.66	1.18
Insurance: Medicare only versus private	1.42	1.03	1.98
Insurance: none versus private	0.76	0.43	1.35
Insurance: unknown versus private	1.04	0.59	1.81
Tumor size: 0.51-1 cm versus 0.5 cm or less	2.46	0.93	6.57
Tumor size: 1.01-1.99 cm versus 0.5 cm or less	**0.13**	0.08	0.22
Tumor size: 2.0 - 4.9 cm versus 0.5 cm or less	**0.26**	0.15	0.44
Tumor size: 5 cm or greater versus 0.5 cm or less	**0.21**	0.11	0.38
Tumor size: Unknown versus 0.5 cm or less	**0.08**	0.03	0.19
Tumor grade (I-IV or unknown)	**1.18**	1.07	1.30
ER Status (positive versus negative)	1.12	0.84	1.49
PR Status (positive versus negative)	0.99	0.75	1.31

Table F2d. Guideline-Concordant Chemotherapy Regimen Model. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Specific Treatment Receipt for All Covariates

Stage I, II, and III Breast Cancer Patients from the POC-BP Study (2004)

Effect	OR	95% Wald Confidence Limits	
BMI < 18.5 versus 18.5-24.9	0.81	0.46	1.43
BMI 25.0-29.9 versus 18.5-24.9	0.85	0.69	1.06
BMI 30.0-34.9 versus 18.5-24.9	0.90	0.69	1.17
BMI ≥ 35 versus 18.5-24.9	0.92	0.70	1.21
Age (years)	**1.03**	1.03	1.04
Comorbidity level (0-3)	1.10	0.96	1.25
Education (lower versus higher, census tract level)	0.87	0.69	1.09
Poverty (higher vs. lower, census tract level)	0.85	0.65	1.12
Urbanicity (100% urban versus 100% rural)	1.07	0.81	1.40
Urbanicity (mixed urban-rural versus 100% rural)	1.30	0.97	1.76
Insurance: Medicaid versus private	0.94	0.73	1.21
Insurance: Medicare only versus private	1.23	0.94	1.61
Insurance: none versus private	**0.59**	0.37	0.93
Insurance: unknown versus private	1.23	0.73	2.10
Tumor size: 0.51-1 cm versus 0.5 cm or less	0.75	0.41	1.37
Tumor size: 1.01-1.99 cm versus 0.5 cm or less	**0.08**	0.05	0.14
Tumor size: 2.0 - 4.9 cm versus 0.5 cm or less	**0.11**	0.07	0.19
Tumor size: 5 cm or greater versus 0.5 cm or less	**0.11**	0.06	0.20
Tumor size: Unknown versus 0.5 cm or less	**0.07**	0.03	0.17
Tumor grade (I-IV or unknown)	1.05	0.99	1.11
ER Status (positive versus negative)	**1.33**	1.05	1.70
PR Status (positive versus negative)	1.06	0.83	1.35

Table F2e. Guideline-Concordant Hormonal Therapy Model. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Specific Treatment Receipt for All Covariates

Stage I, II, and III Breast Cancer Patients from the POC-BP Study (2004)

Effect	OR	95% Wald Confidence Limits	
BMI < 18.5 versus 18.5-24.9	1.31	0.56	3.09
BMI 25.0-29.9 versus 18.5-24.9	0.88	0.70	1.10
BMI 30.0-34.9 versus 18.5-24.9	1.12	0.86	1.46
BMI ≥ 35 versus 18.5-24.9	1.21	0.87	1.69
Age (years)	**0.99**	0.98	1.00
Comorbidity level (0-3)	1.01	0.88	1.15
Education (lower versus higher, census tract level)	1.03	0.82	1.30
Poverty (higher vs. lower, census tract level)	**0.71**	0.54	0.94
Urbanicity (100% urban versus 100% rural)	0.89	0.66	1.20
Urbanicity (mixed urban-rural versus 100% rural)	1.22	0.89	1.68
Insurance: Medicaid versus private	0.79	0.59	1.06
Insurance: Medicare only versus private	1.10	0.82	1.47
Insurance: none versus private	1.00	0.54	1.86
Insurance: unknown versus private	1.46	0.82	2.59
Tumor size: 0.51-1 cm versus 0.5 cm or less	1.28	0.88	1.87
Tumor size: 1.01-1.99 cm versus 0.5 cm or less	**1.53**	1.08	2.15
Tumor size: 2.0 - 4.9 cm versus 0.5 cm or less	**1.71**	1.22	2.41
Tumor size: 5 cm or greater versus 0.5 cm or less	**1.61**	1.05	2.48
Tumor size: Unknown versus 0.5 cm or less	1.11	0.50	2.47
Lymph node status (any positive versus all negative)	1.02	0.83	1.26
Tumor grade (I-IV or unknown)	1.01	0.95	1.07

Table F2f. Overall Guideline-Concordant Therapy Model. Odds Ratios (OR) and 95% Confidence Intervals (CI) of Specific Treatment Receipt for All Covariates

Stage I, II, and III Breast Cancer Patients from the POC-BP Study (2004)

Effect	OR	95% Wald Confidence Limits	
BMI < 18.5 versus 18.5-24.9	0.55	0.29	1.04
BMI 25.0-29.9 versus 18.5-24.9	0.87	0.72	1.06
BMI 30.0-34.9 versus 18.5-24.9	1.11	0.88	1.40
BMI ≥ 35 versus 18.5-24.9	1.14	0.89	1.47
Age (years)	**0.99**	0.99	1.00
Comorbidity level (0-3)	0.99	0.87	1.12
Education (lower versus higher, census tract level)	0.81	0.65	1.01
Poverty (higher vs. lower, census tract level)	**0.76**	0.60	0.97
Urbanicity (100% urban versus 100% rural)	0.99	0.76	1.29
Urbanicity (mixed urban-rural versus 100% rural)	1.24	0.96	1.61
Insurance: Medicaid versus private	**0.70**	0.54	0.91
Insurance: Medicare only versus private	1.22	0.96	1.54
Insurance: none versus private	**0.65**	0.42	1.00
Insurance: unknown versus private	1.28	0.76	2.15
Tumor size: 0.51-1 cm versus 0.5 cm or less	**1.81**	1.28	2.57
Tumor size: 1.01-1.99 cm versus 0.5 cm or less	**0.73**	0.54	0.98
Tumor size: 2.0 - 4.9 cm versus 0.5 cm or less	0.76	0.56	1.05
Tumor size: 5 cm or greater versus 0.5 cm or less	0.85	0.55	1.31
Tumor size: Unknown versus 0.5 cm or less	0.67	0.31	1.49
Tumor grade (I-IV or unknown)	0.98	0.93	1.03

Aim 3 Hazards Ratios (Shown in Table 3 of Chapter 6)

Table F3a. Overall Mortality Model Including Guideline Concordance Variable. Hazard Ratios (OR) and 95% Confidence Intervals (CI) for All Covariates

Stage I, II, and III Breast Cancer Patients from the POC-BP Study (2004)

Effect	HR	95% Wald Confidence Limits		p-value[1]
BMI < 18.5 versus 18.5-24.9	1.12	0.59	2.12	0.73
BMI 18.5-24.9	1.00	.	.	.
BMI 25.0-29.9 versus 18.5-24.9	0.84	0.66	1.06	0.14
BMI 30.0-34.9 versus 18.5-24.9	**0.77**	0.59	0.99	0.04
BMI ≥ 35 versus 18.5-24.9	0.88	0.67	1.15	0.34
Overall Guideline-Concordant Treatment	**0.65**	0.54	0.80	< 0.001
Age (years)	1.03	1.02	1.04	<.0001
Tumor Stage (III versus I, AJCC staging criteria)	3.74	2.98	4.69	<.0001
Tumor Stage (II versus I, AJCC staging criteria)	1.48	1.19	1.85	< 0.001
Tumor Stage I (AJCC staging criteria)	1.00	.	.	.
Comorbidity level (0-3)	**1.46**	1.29	1.65	< 0.001
Tumor grade (2 versus 1)	1.07	0.81	1.41	0.65
Tumor grade (3 versus 1)	**1.88**	1.44	2.46	<.0001
Tumor grade (4 versus 1)	1.19	0.51	2.80	0.69
Tumor grade (unknown versus 1)	1.14	0.74	1.77	0.55
Tumor grade 1	1.00	.	.	.
ER Status (positive versus negative)	0.88	0.69	1.12	0.30
PR Status (positive versus negative)	0.83	0.67	1.05	0.12
Insurance: Medicaid versus unknown	1.07	0.60	1.93	0.81
Insurance: Medicare only versus unknown	0.95	0.55	1.66	0.87
Insurance: none versus unknown	1.35	0.69	2.67	0.38
Insurance: private versus unknown	0.66	0.38	1.14	0.14
Insurance: unknown	1.00	.	.	.
Education (lower versus higher, census tract level)	1.06	0.83	1.36	0.63
Poverty (higher vs. lower, census tract level)	0.91	0.69	1.19	0.48
Urbanicity (100% urban versus 100% rural)	0.94	0.72	1.23	0.65
Urbanicity (mixed urban-rural versus 100% rural)	1.08	0.81	1.45	0.58
Urbanicity: 100% rural	1.00	.	.	.

1. p-value from analysis of maximum likelihood estimates.

Table F3b. Breast Cancer Mortality Model Including Guideline Concordance Variable. Hazard Ratios (OR) and 95% Confidence Intervals (CI) for All Covariates

Stage I, II, and III Breast Cancer Patients from the POC-BP Study (2004)

Effect	HR	95% Wald Confidence Limits		p-value[1]
BMI < 18.5 versus 18.5-24.9	0.33	0.10	1.07	0.06
BMI 18.5-24.9	1.00	.	.	.
BMI 25.0-29.9 versus 18.5-24.9	0.87	0.62	1.23	0.44
BMI 30.0-34.9 versus 18.5-24.9	0.99	0.69	1.42	0.96
BMI ≥ 35 versus 18.5-24.9	0.91	0.61	1.36	0.64
Overall Guideline-Concordant Treatment	**0.75**	0.58	0.99	0.04
Age (years)	0.99	0.98	1.01	0.34
Tumor Stage (III versus I, AJCC staging criteria)	**10.08**	6.85	14.83	<.0001
Tumor Stage (II versus I, AJCC staging criteria)	**2.50**	1.65	3.78	<.0001
Tumor Stage I (AJCC staging criteria)	1.00	.	.	.
Comorbidity level (0-3)	1.08	0.88	1.33	0.48
Tumor grade (2 versus 1)	**2.16**	1.04	4.49	0.04
Tumor grade (3 versus 1)	**5.52**	2.71	11.24	<.0001
Tumor grade (4 versus 1)	**3.69**	1.05	12.96	0.04
Tumor grade (unknown versus 1)	2.27	0.91	5.66	0.08
Tumor grade 1	1.00	.	.	.
ER Status (positive versus negative)	0.84	0.59	1.19	0.32
PR Status (positive versus negative)	0.71	0.51	0.99	0.04
Insurance: Medicaid versus unknown	0.99	0.47	2.05	0.97
Insurance: Medicare only versus unknown	1.05	0.50	2.21	0.91
Insurance: none versus unknown	0.92	0.40	2.15	0.85
Insurance: private versus unknown	0.72	0.35	1.46	0.36
Insurance: unknown	1.00	.	.	.
Education (lower versus higher, census tract level)	0.99	0.69	1.41	0.95
Poverty (higher vs. lower, census tract level)	1.09	0.74	1.61	0.66
Urbanicity (100% urban versus 100% rural)	0.90	0.60	1.34	0.60
Urbanicity (mixed urban-rural versus 100% rural)	1.12	0.73	1.73	0.60
Urbanicity: 100% rural	1.00	.	.	.

1. p-value from analysis of maximum likelihood estimates.

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