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Comorbidity and Body Mass Index (BMI) as Predictors of Survival for African Americans and Caucasians Following Surgery for Adenocarcinoma of the Colon

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COMORBIDITY AND BODY MASS INDEX (BMI) AS PREDICTORS OF SURVIVAL FOR AFRICAN AMERICANS AND CAUCASIANS FOLLOWING SURGERY FOR ADENOCARCINOMA OF THE COLON

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EPIDEMIOLOGY

ABSTRACT

There is a survival disparity between African Americans and Caucasians having colon cancer. Among the reasons given as possible causes for the increased risk of death in African Americans following a diagnosis of colon cancer are comorbidity and body habitus. The primary question this dissertation sought to answer was whether or not comorbidity and/or BMI could account for any of the increased risk of death seen in African Americans with colon cancer. However, before answering this question, the matter of which comorbidity index to use in assessing the comorbidity burden in this population of colon cancer patients had to be addressed.

The study population consisted of colon cancer patients (n = 496) who underwent surgery at the University of Alabama at Birmingham (UAB) Hospital from 1981-2002. In the first manuscript, hazard ratios (HR) with 95% confidence intervals (CI) were obtained by Cox proportional hazards models for the three comorbidity indices and the association with death. In the second manuscript, hazard ratios were obtained for the

association of race, comorbidity, BMI, and covariates with mortality. The confounding influence of comorbidity and BMI for the increased risk of death associated with African American race was evaluated. Effect modification by tumor stage and race was also assessed.

In the comparison of the three comorbidity indices, the highest comorbidity burden for each index was significantly associated with poorer overall survival (ACE-27: HR = 1.63, 95% CI, 1.24-2.15; NIA/NCI: HR = 1.83, 95% CI, 1.29-2.61; CCI: HR = 1.46, 95% CI, 1.14-1.88). For BMI, with those of normal weight serving as the referent group, being underweight increased the risk of death (HR = 1.54; 95% CI, 0.96-2.45) while being overweight/obese was protective (HR = 0.77; 95% CI, 0.61-0.97). After adjustment for comorbidity, BMI, and other risk factors, African American race was still associated with a 34% increased risk of death relative to Caucasians (HR = 1.34; 95% CI, 1.06-1.68).

Comorbidity and BMI are both associated with death following surgery for colon cancer. However, neither comorbidity nor BMI accounts for any of the excess mortality associated with African American race.

DEDICATION

To Lynley, Davis, and Sanders.

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INTRODUCTION

Colon cancer is a significant public health issue in that colon cancer ranks third among all cancers in terms of incidence and mortality among both men and women in the United States. In 2008, it was estimated that there were 108,000 new cases of colon cancer and 50,000 deaths due to colorectal cancer (CRC).[1] Despite these frightening statistics, these numbers represent a declining public health impact of colon cancer over the past 25 years due to a decreasing incidence as well as better survival due to earlier detection and improved treatment.[2-4]

Racial Disparity in Colon Cancer Survival: A Public Health Problem

Though the statistics associated with colon cancer have been improving over the past two to three decades, there has been a widening racial disparity in survival during this time period between non-Hispanic African Americans and non-Hispanic Caucasians. Indeed, African Americans have worse survival for nearly all cancers, and colon cancer is no exception. This fact is illustrated when looking at five-year relative survival rates for three time periods from 1975-2003. For the years 1975-77, Caucasians experienced a 6% absolute survival advantage (Caucasians = 52%; African Americans = 46%). For the years 1984-86, the absolute difference in five-year relative survival had increased to 10% (Caucasians = 60%; African Americans = 50%). Finally, for the period 1996-2002, the absolute difference in survival had increased to 12% (Caucasians = 66%; African Americans = 54%). From the statistics above reported by Jemal et al,[1] it is evident that

the increasing difference in survival has been due to Caucasians experiencing a greater increase in five-year relative survival as well as having a higher baseline survival (1975-77) compared to African Americans.

Racial Disparity in Survival: Reasons

A number of possible scenarios have been postulated and studied in an effort to account for the increased risk of death among African Americans. Investigators have suggested that differences between African Americans and Caucasians in access to health-care, exposure to risk factors (e.g. obesity), stage at diagnosis, comorbidity, the physician-patient relationship, socioeconomic status, and tumor characteristics may explain the observed racial difference in survival.[1, 5-9] However, the degree to which these factors operate in determining survival remains unclear.

The Evidence: Tumor Stage

Using Surveillance, Epidemiology, and End Results (SEER) data for the years 1996-2003 for colon cancer, Caucasians are more likely than African Americans to be diagnosed with a localized tumor (38% v. 33%). Conversely, African Americans are more likely to be diagnosed with distant tumors (26% v. 20%).[4] Differences in stage at diagnosis is the most important factor in explaining survival differences between Caucasians and African Americans.[7] The Black/White Cancer Survival Study[10] (BWCSS) found that the excess mortality associated with black race decreased by 60%

after adjusting for stage though a 20% increased risk remained. Other studies have found similarly increased risks of mortality for African Americans.[6, 11-17] However, when looking at mortality rates by stage, African Americans still have lower 5-year relative survival compared to Caucasians: for localized stage, 92% v. 85% (Caucasians v. African Americans); for regional stage, 70% v. 63%; and for distant stage, 11% v. 8%.[18] Thus, stage alone does not account for the disparity in survival among Caucasians and African Americans.

The Evidence: Comorbidity

Comorbidity is defined as the presence of other diseases in conjunction with an index disease of primary interest. The study of comorbidity is important because comorbid conditions in the cancer patient can impact the timing of cancer detection, treatment, prognosis, and outcome.[19] As comorbid conditions can exert their effects at multiple levels along the spectrum of care for the cancer patient, failure to account for comorbidity in cancer studies could result in confounding bias.[20] In addition, the prevalence of comorbid conditions increases with age.[21] As sporadic (without an identifiable genetic cause) colon cancer is a disease of older age (the mean age at diagnosis is 71), examining the impact of comorbidity should be viewed as an integral component in cancer studies. The incorporation of comorbidity measurement and assessment into cancer research will result in more accurate prognosis and tailored therapy for patients with cancer.

Comorbidity can act in two opposing ways to impact detection of the tumor. One line of reasoning suggests that the presence of comorbid conditions increases encounters with clinicians and thus, increases opportunities for screening and incidental cancer detection. Cooper et al, as part of the Direct Observation of Primary Care (DOPC) study, found that primary care physicians perform preventive services for 33% of office visits.[22] Two studies found that the presence of chronic conditions increased the likelihood of screening for CRC.[23, 24]

One the other hand, comorbidity may act as a barrier to screening. Some authors have suggested that the symptoms of comorbid conditions may conceal the effects of the cancer, leading to delayed diagnosis.[25, 26] Treating comorbid conditions may be taxing in terms of the time demands on primary care physicians such that screening for CRC is seen as less important.[27] Lastly, cancer screening may be seen as less of a priority when considered in the context of other causes of morbidity and mortality.[28] Two studies of breast cancer screening and one of breast and cervical cancer screening found that comorbidity level was inversely associated with being screened for cancer.[29-31]

Several studies have found that comorbidity negatively impacts survival in colon cancer patients. The most commonly used instrument to measure comorbidity is the Charlson Comorbidity Index (CCI), either in its original form or a slightly modified version.[19, 32] De Marco et al[33] used the CCI and found that having one or more comorbid conditions was negatively associated with short-term survival, especially among those 70 years of age or older. Also using the CCI, Rieker et al[34] noted that having 3 or more comorbid conditions was associated with cancer-specific death and death from any cause among a population of CRC patients in Germany. Ouellette et al[35] reported that CRC

patients with more comorbidity as measured by the CACI (Charlson-Age Comorbidity Index) were at increased risk for cancer-related death. Lemmens et al[36] utilized a modified version of the CCI and observed that, not only was comorbidity related to increased overall mortality for colon cancer patients, but it was also related to a decreased likelihood of receiving recommended adjuvant chemotherapy for stage III patients. In a National Institute on Aging (NIA) and NCI collaborative study, Yancik et al[37] developed a new comorbidity index. These investigators reported that increasing total comorbidity was associated with increasing risk of death from any cause.

As noted previously, some investigators have speculated that higher comorbidity burden in African Americans compared to their Caucasian counterparts may be responsible for the decreased survival following a diagnosis of colon cancer. Though the above studies have shown that comorbidity is associated with mortality among colon cancer patients, only two studies have evaluated the confounding influence of comorbidity in an effort to explain the increased risk of death for African Americans following a diagnosis for colon cancer. Mayberry et al,[10] as part of the aforementioned National Cancer Institute Black/White Cancer Survival Study, found that African Americans had an increased risk of colon cancer-specific as well as all-cause mortality. The addition of comorbidity to a model containing tumor stage did not result in a further reduction of the hazard ratio associated with African American race. Thus, comorbidity did not explain any of the increased risk of death associated with African Americans. A weakness of this study was that no mention was made as to how comorbidity was defined. A more recent study by Gomez et al[38] also investigated comorbidity in an effort to explain the disparity in survival between African Americans and Caucasians with

colorectal cancer. In this study which utilized SEER data, the authors found that comorbidity independently predicted shorter survival, but comorbidity did not explain the survival disparity between blacks and whites. However, the authors did find varying effects of comorbidity in predicting all-cause mortality when analyses were stratified by race. A weakness of this study was the use of administrative data (Medicare claims) in the assessment of comorbidity information.

The Evidence: Body Mass Index

Many studies have found a positive association between increased body mass index and risk for colon cancer.[39, 40] The consensus on this issue is that obesity increases the risk of getting colon cancer though the evidence is stronger for men than women. Few studies have examined the role of obesity by race and the relationship with colon cancer or CRC. The Cancer Prevention Study II[41] found an increased risk of mortality due to colon cancer with increasing body mass index among men and an increased risk among women in the highest category of BMI. These investigators found no effect modification by race, but African Americans were more likely to be in the highest category of BMI, especially among women. In a case-control study, Satia-Abouta et al[42] found that African American cases were more likely to be obese than Caucasians though the focus of the study was total energy and macronutrients.

Though the subject of obesity and risk for colon cancer has been the subject of numerous investigations, few studies have examined the role of obesity and its relation to survival after diagnosis of colon cancer. The earliest study of BMI and survival

following a diagnosis of colon cancer was conducted by Slatttery et al[43] using patients from the Utah Cancer Registry. These investigators found that BMI was not a significant predictor of mortality. A weakness of this study was the fact that standardized cut-points for BMI were not used. Meyerhardt et al[44] reported that, among men and women with stage II & III colon cancer enrolled in a clinical trial, underweight men experienced an increased risk of overall mortality though for women, obesity was associated with an increased risk of death. As part of the National Surgical Adjuvant Breast and Bowel Project (NSABP), Dignam et al[45] reported that, among patients with Dukes B and C colon cancer, underweight participants were at increased risk of non-colon cancer-related deaths and very obese participants were at increased risk of death due to colon cancer. Doria-Rose et al[46] conducted a study to assess the effect of BMI on survival following colon cancer diagnosis among post-menopausal women in Wisconsin. An increased risk of death due to colon cancer was found among both underweight and overweight women. Last, in an Australian study by Haydon et al,[47] BMI was not associated with overall or disease-specific survival though other measures of obesity were associated with an increased risk of death. No association with underweight was investigated in this study as both underweight and normal weight participants served as the referent group. To our knowledge, no study has investigated body habitus in an effort to explain the increased risk of death for African Americans having colon cancer.

Implications of Current Research

The work presented in this dissertation will address several issues and add important contributions to the epidemiological literature. In cancer studies as well as other areas of research, when designing a study in which comorbidity is either a variable of interest or simply to be accounted for in the statistical analysis, one must decide how to measure comorbidity. An issue that has not been fully explored is whether or not the results of a study vary according to the index of comorbidity chosen to assess comorbidity burden. In the first paper presented in this dissertation, the comorbidity burden of a population of patients who underwent surgery for colon cancer was assessed using three indices of comorbidity: the Adult Comorbidity Evaluation-27 (ACE-27), the National Institute on Aging and National Cancer Institute (NIA/NCI) Comorbidity Index, and the Charlson Comorbidity Index (CCI). The aims of this study were to emphasize the importance of comorbidity assessment in cancer research, assess the prognostic ability of the three comorbidity indices in predicting death due to any cause, and to qualitatively compare the point estimates obtained for other risk factors according to comorbidity index.

The second paper presented in this dissertation addresses the topic of survival disparity between African Americans and Caucasians with colon cancer. The aims for this aspect of the dissertation were to: assess the role of comorbidity and body habitus with survival following surgery for colon cancer, investigate the potential confounding influence of comorbidity and BMI as an explanation for the decreased survival of African Americans with colon cancer relative to Caucasians, and examine effect modification by race and tumor stage for the association of comorbidity and BMI with mortality in order

to increase our understanding of how these risk factors determine survival within race and according to tumor status.

COMORBIDITY INDICES ARE ASSOCIATED WITH MORTALITY FOLLOWING SURGERY FOR COLON CANCER

By

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Abstract

Background. For cancer patients, comorbidity can impact the time of cancer detection, treatment, and prognosis. This study compared the association of comorbidity with all-cause mortality following surgery for colon cancer utilizing three comorbidity indexes: the Adult Comorbidity Evaluation- 27 (ACE-27), the National Institute on Aging (NIA) and National Cancer Institute comorbidity index, and the Charlson Comorbidity Index (CCI).

Methods. The study population consisted of colon cancer patients (n = 496) who underwent surgery at the University of Alabama at Birmingham (UAB) Hospital from 1981-2002. Hazard ratios (HR) with 95% confidence intervals (CI) were obtained by Cox proportional hazards models for the three comorbidity indexes in predicting overall survival. We compared the point estimates obtained for comorbidity and other risk factors across the three models.

Results. The highest comorbidity burden for each index was significantly associated with poorer overall survival (ACE-27: HR = 1.63, 95% CI, 1.24-2.15; NIA/NCI: HR = 1.83, 95% CI, 1.29-2.61; CCI: HR = 1.46, 95% CI, 1.14-1.88). There was little variation in the point estimates for the other risk factors across the three models.

Conclusions. All three indices of comorbidity significantly added to the predictive ability of a model containing other risk factors. In addition, the results obtained utilizing the three indices of comorbidity were strikingly similar. The decision to use a particular comorbidity index should be guided by the goals of the study, the data available to the investigator, and the resources necessary to acquire the data.

Introduction

Colon cancer is the third ranking cancer in terms of incidence and mortality among men and women in the United States.[1] Despite these ominous statistics, the public health impact associated with colon cancer has improved over the last 25 years due to decreasing incidence as well as better survival due to earlier detection and improved treatment.[2-4] In order to provide the best therapy possible to patients with this disease, treatment should be tailored to the individual patient, taking into account the patient's age and overall health. Physicians subjectively do this when prescribing treatment for individual patients, but objective methods for tailoring treatment plans are usually not employed.[5] One way to stratify patients with colon cancer beyond known risk factors for mortality such as age, tumor stage, and tumor grade is comorbidity. Comorbidity is defined as the presence of other diseases in conjunction with an index disease (e.g. colon cancer) of primary interest.[6] Studies have shown that increasing comorbidity burden decreases the likelihood of receiving adjuvant chemotherapy when it is indicated.[7, 8] However, the use of comorbidity indices to guide treatment decisions is not common practice due to lack of evidence from clinical trials which generally restrict entry of patients with chronic comorbid conditions. By utilizing a comorbidity index, physicians would have greater information at their disposal to decide on the best treatment options for each patient. There are several comorbidity indices that have been used in studies of cancer research. However, few studies have evaluated the predictive ability of different comorbidity indices in an effort to determine whether or not the conclusions reached differ according to comorbidity index.

In addition to the rationale above, there are other reasons that highlight the importance of comorbidity assessment. One that directly relates to treatment in the cancer patient concerns eligibility for clinical trials. Older patients with comorbidity are often excluded from involvement in clinical trials.[9] However, most patients diagnosed with colon cancer are ≥ 65 years of age and also have comorbid conditions at the time of cancer diagnosis.[10, 11] The rationale for excluding these patients is to eliminate the confounding influence of comorbidity in the evaluation of treatment efficacy. However, by excluding older patients with comorbidities, the conclusions drawn from clinical trials may not be directly generalizable to the majority of patients with colon cancer.[12] Potential toxicity with the study treatment regimen has been consistently cited by physicians as a reason to not enroll older patients with comorbidities.[12] The assessment of comorbidity among patients enrolled in clinical trials would identify those patients at higher risk of toxicity. In addition, investigators could compare the efficacy of a given treatment regimen across differing levels of comorbidity burden. Therefore, comorbidity assessment in clinical trials would allow for more accurate estimates of prognosis for a given patient receiving treatment and also prevent certain patients with colon cancer from being denied a beneficial treatment regimen.

Another issue that calls for comorbidity assessment in cancer patients concerns research studies where comorbidity may operate as a confounder.[13] Though comorbidity may not be the focus of a particular study, failing to account for comorbidity in the statistical analysis may result in erroneous conclusions regarding the parameters of interest. As comorbidity is associated with morbidity and mortality in cancer patients, good research practice dictates that it should be assessed in studies of cancer outcomes.[14]

In this study, we compared the results obtained for three comorbidity indexes in predicting mortality following surgery for colon cancer: the Adult Comorbidity Evaluation-27 (ACE-27), the Charlson Comorbidity Index (CCI), and the National Institute on Aging (NIA) and National Cancer Institute (NCI) comorbidity index.[11, 15-17] The aims of this study were to emphasize the importance of comorbidity assessment in cancer research, assess the prognostic ability of the three comorbidity indexes in predicting death due to any cause in a population of colon cancer patients, and to qualitatively compare the point estimates obtained for other risk factors according to comorbidity index. The results of this study will answer the question as to whether selection of one index of comorbidity versus another can lead to differing conclusions.

Methods

Our study population consisted of patients who underwent surgery for sporadic (non-genetic) adenocarcinoma of the colon at The University of Alabama at Birmingham (UAB) Hospital from 1981-2002. The termination date for the accrual of follow-up information was June 1, 2008. The initial patient population was comprised of 631 participants. In order to be eligible for this study, the diagnosis of first primary colon cancer had to be the earliest diagnosis of any cancer in the patient (with the exception of non-melanoma skin cancer). Therefore, we excluded patients previously diagnosed with other cancers (n = 63). We also excluded subjects with more than one primary tumor (n = 13) and those with unknown tumor grade (n = 3). As the primary aim of this study was to assess the effect of comorbidity on survival, and as the impact of comorbidity

increases as one ages, we excluded patients who were less than 40 years of age (n = 22). By excluding patients less than 40, we also minimized the probability of the tumor having a genetic cause as such tumors tend to occur at younger ages compared to non-genetic tumors.[18] We removed from our study population those patients who died of complications following surgery by excluding subjects who survived less than one month after tumor resection (n = 21). We also excluded patients who were citizens of other countries or originally from other countries (n = 7). Lastly, we excluded 6 participants with missing height information which precluded assessment of Body Mass Index (BMI). After the above exclusions were made, our study sample consisted of 496 patients. This study was approved by the Institutional Review Board (IRB) at UAB.

Demographic, clinical, and patient information regarding age at time of surgery, gender, race, surgery date, insurance status, smoking status, and perioperative variables was obtained from medical records. Age was treated as a continuous variable. Year of surgery was categorized in 5 to 6 year intervals based on the distribution of patients from 1981-2002. Smoking information was recorded as current, former, or never smoked. Insurance status was recorded as whether or not the patient had private insurance coverage. We also recorded BMI $\left[BMI = \frac{weight\ (kg)}{height\ (m)^2}\right]$ at the time of surgery, the presence of bowel obstruction, and whether the participant received any blood transfusions during surgery.

Tumor specific characteristics were obtained from pathology reports and adjudicated by two of the investigators (CS, UM). Tumors were classified by the tumor-node-metastasis (TNM) system and staged according to the American Joint Committee

on Cancer (AJCC) staging system as Stages I, II, III, and IV.[19] Tumor grade was recorded as well differentiated, moderately differentiated, poorly differentiated, or unknown (there were no tumors graded as undifferentiated). As suggested by Compton et al, well and moderately differentiated tumors were referred to as "low" grade, and poorly differentiated tumors were designated as "high" grade.[20]

Comorbidity information was abstracted from the medical record up to the date of surgery by the primary author (RH). This data was obtained from several sources in the medical record including physician notes, anesthesia notes, nursing notes, and discharge summaries. Based on their comorbidity burden, patients were categorized using the three indices of comorbidity: the ACE-27 index, the NIA/NCI comorbidity index, and the CCI. As having a previous cancer was an exclusion criterion for this study, information pertaining to cancer was not used in the calculation of comorbidity burden. For the ACE-27 index, each subject was given an overall grade of none, mild, moderate, or severe comorbidity as detailed by the Piccirillo et al.[21] Using the CCI, patients were categorized based on the sum of weighted comorbidities into three groups: 0, 1, and ≥ 2 as has been done previously.[22] Finally, in obtaining a total comorbidity count for the NIA/NCI measure of comorbidity, patients were placed into four groups corresponding to the total number of comorbid conditions: 0-1, 2-3, 4-5, ≥ 6. This categorization was based on the distribution within the study population. We slightly modified the list of comorbid conditions for the NIA/NCI index by excluding anemia as a comorbid condition as it is a common symptom of colon cancer. We also excluded smoking information as part of the comorbidity assessment for the NIA/NCI index because this information was recorded as a separate variable.

Follow up data was obtained on each subject from the UAB tumor registry. This information is updated every 6 months for each patient by contacting the patient or a family member. If a patient has died since the last follow up contact, the date of death is recorded though cause of death is not obtained. Patients that were still alive at the termination date of the study are right censored at the last contact date. If a patient was recorded as alive and ≥ 3 years had elapsed since the last contact, the patient was designated as "lost to follow up."

Statistical Analysis

Survival time was calculated from the date of surgery until death, the termination date of the study, or the last date of contact for patients that were still alive. The event of interest was death from any cause. All reported p values are two-sided, and statistical significance was defined as $p < 0.05$.

The Cox proportional hazards (PH) model was used to obtain hazard ratios (HR) with 95% confidence intervals (CI) for the bivariate association of risk factors and other covariates with all-cause mortality. For categorical variables (surgery date, smoking status, comorbidity, tumor stage, and BMI), the statistical significance for the overall association of the variable with mortality was obtained by the likelihood ratio test. Multivariable models were constructed for each of the three comorbidity indices. For variable selection, we considered variables that were associated with mortality at $p < 0.20$ as potential confounders and included them in the initial multivariable model for each comorbidity index. In order to obtain the final multivariable model, the least significant variable was removed in a stepwise manner for each of the three models. If a covariate

was significant in any of the three models, it was retained in all models. This process ensured that the final model for all three comorbidity indices would contain the same variables and therefore, allow comparison of ratio measures across the three models. After obtaining the final model for each of the three comorbidity indices, the proportional hazards assumption was evaluated and met for each comorbidity index by testing the interaction with time.

Results

Study Population

The characteristics of the study population and the bivariate association of each characteristic with survival are shown in Table 1. Most subjects were deceased at the end of the follow-up period (n = 333, 67.1%). The median follow up time for all study participants was nearly 5 years (58.2 months). With respect to demographic characteristics, the mean age (66.9 ± 12.2 years) of our study participants at the time of surgery reflects the fact that colon cancer is a disease of older age. There were more females (n = 271, 54.6 %) than males and Caucasians (n = 303, 61.2%) than African Americans in our study population. Greater numbers of our study population were accrued during the latter years of the study entry period (1992-2002: n = 324, 65.3%). Most of our study population had a private insurance carrier (n = 334, 67.6%) and never smoked (n = 297, 59.9%). Only 28 study participants (5.7%) were designated as "lost to follow-up" (data not shown).

In comparing the three comorbidity indexes, the majority of study participants had no comorbidity or mild comorbidity though differences are apparent based on the categorization for each index. For tumor characteristics, the majority of our patients had localized disease (stages I & II: n = 260, 52.5%) and histologically, most tumors were low grade (n = 398, 80.2 %). Perioperatively, most subjects were normal/overweight (n = 367, 74.0%), bowel obstruction was present in 29.6% (n = 147) of patients, and a small proportion (n = 25, 5.0%) of patients received blood transfusions during surgery.

Bivariate Associations with Mortality

Unadjusted hazard ratios were obtained by Cox PH models for each of the characteristics shown in Table 1. Age was significantly associated with death due to any cause with each 10-year increase in age conferring a 25% increased risk of mortality (HR = 1.25; 95% CI, 1.14–1.37). There was a 23% increased risk of death associated with African American race (HR = 1.23; 95% CI, 0.99–1.53) that was borderline statistically significant. The years following the earliest period of entry into the study were associated with a decreased risk of mortality (1981-86 v. 1987-2002: HR = 1.42; 95% CI, 1.09-1.85). Lack of private insurance also increased the risk of death (HR = 1.26; 95% CI, 1.01–1.58). Gender and smoking status were not associated with the outcome.

The same conclusions were drawn for the three comorbidity indices in that the highest comorbidity burden was associated with worse survival. In addition, the hazard ratios for the most severe category for the three indexes were similar. For the ACE-27 index, the severe category of comorbidity was associated with a 56% increased risk of

death (HR = 1.56; 95% CI, 1.11–2.20). Those with CCI score of ≥ 2 had a 58% increased risk of death (HR = 1.58; 95% CI, 1.21–2.05), and the highest level of comorbidity in the NIA/NCI index conferred a 56% increased risk (HR = 1.56; 95% CI, 1.06–2.29).

For tumor-related and treatment characteristics, tumor stage was significantly associated with survival. Compared to study participants with stage I tumors: patients with stage II tumors had a 43% increased risk of death (HR = 1.43; 95% CI, 1.00–2.05), stage III tumors were associated with a 2.5-fold increased risk (HR = 2.48; 95% CI, 1.72–3.58), and stage IV tumors had a 9.4-fold increased risk of death due to any cause (HR = 9.37; 95% CI, 6.40–13.71). For tumor grade, high grade tumors increased the risk of death by 70% (HR = 1.70; 95% CI, 1.32–2.20). Perioperatively, compared to those of normal weight, being underweight was associated with an increased risk of death (HR = 1.81; 95% CI, 1.15–2.83) though being overweight (HR = 0.86; 95% CI, 0.67–1.11) or obese (HR = 0.77; 95% CI, 0.57–1.03) was protective. The presence of bowel obstruction increased the risk of death nearly two-fold (HR = 1.98; 95% CI, 1.58–2.48) as did receiving blood during surgery (HR = 1.96; 95% CI, 1.26–3.06).

Multivariable models

Cox proportional hazards models were constructed separately for the three comorbidity indices. Based on the results obtained from the unadjusted association of each risk factor with survival, we combined categories when the hazard ratios were similar. Therefore, we combined strata for comorbidity, tumor stage, and BMI. The

results of the multivariable Cox regression models are shown in Table 2 for each comorbidity index. As was the case for the unadjusted measures, only the highest level of comorbidity in each model was associated with survival. The highest level (severe) of the ACE-27 index increased the risk of death by over 60% (HR = 1.63; 95% CI, 1.24–2.15). A stronger association was found when comparing the highest level of the NIA/NCI index (≥ 6) (HR = 1.83; 95% CI, 1.29–2.61) to those with lower comorbidity burden though the confidence interval here is wider reflecting the small number of participants in this category (n = 44). An increased risk was found among those with a score of ≥ 2 by the CCI though the magnitude of association was the smaller compared to the other two indices (HR = 1.46; 95% CI, 1.14–1.88).

Nearly identical results were obtained when comparing the range of hazard ratios for the other risk factors across each model. The association with African American race was equivalent (HR_{range}; 1.34-1.36) and statistically significant in all models. The results obtained for tumor stage were also within a narrow range (Stage III: HR_{range}; 1.95-2.06) (Stage IV: HR_{range}; 8.54-8.96) as were the results for tumor grade (HR_{range}: 1.55-1.66). The results for BMI were virtually identical for underweight (HR_{range}: 1.54-1.56) and overweight/obese (HR_{range}: 0.77-0.80). Lastly, the point estimates obtained for the presence of bowel obstruction were essentially equal (HR_{range}: 1.51-1.54). Surgery date, insurance status, and receiving blood during surgery did not remain statistically significant in the multivariable models.

Discussion

In this study, three comorbidity indices were utilized to assess the comorbidity burden in a population of colon cancer patients just prior to surgery. In a survival model with death due to any cause as the outcome of interest, we compared the point estimates obtained for each comorbidity index as well as other risk factors. All three comorbidity indices were statistically significant for the association with all-cause mortality in this population of colon cancer patients at one institution. In addition, and perhaps more importantly for investigators that are not interested in the effect of comorbidity per se and simply want to adjust for comorbidity in the analysis, the point estimates obtained for the other risk factors in each of the three multivariable models were essentially equivalent. In summary, the conclusions were the same no matter what comorbidity index was used to assess the comorbidity burden in this population of colon cancer patients. Therefore, for future cancer research studies, the decision to use a particular comorbidity index should be guided by the goals of the study, the data available to the investigator, and the resources necessary to acquire the data.

The results of this study have other implications. Comorbidity offers a way to further stratify cancer patients beyond known risk factors such as age and tumor-associated characteristics. Despite the fact that older patients have been shown to benefit from adjuvant therapy, older colon cancer patients are less likely to receive chemotherapy.[23, 24] Though advanced age, in itself, is less often an exclusionary criterion as had been the case in the past, many clinical trials are prohibitively restrictive with regard to comorbidity burden.[25-27] Thus, age becomes a *de facto* exclusion since the number of comorbidities increases with age.[11] By assessing comorbidity among

participants in a clinical trial, researchers would have additional information at their discretion leading to more accurate projections of treatment-related toxicity, drug-drug interactions, and efficacy of a particular chemotherapeutic regimen.[12, 28] This information is currently lacking and thus, older patients with comorbidity may be denied a treatment from which they could benefit.

The results of the present study are consistent with previous results demonstrating the independent prognostic effect of comorbidity on survival among patients with colon or colorectal cancer. Several investigators have used the CCI and demonstrated shorter survival with increasing comorbidity burden.[7, 29-32] The NIA/NCI comorbidity index has been used in only one study of colon cancer. In this study, the highest two levels of comorbidity were associated with an increased risk of death due to any cause.[11] Using the ACE-27 index, Piccirillo et al[21] demonstrated that, for all digestive system tumors, increasing comorbidity was inversely related to survival.

An aim of this study was to compare the results obtained in three survival models utilizing three distinct comorbidity indices among a population of colon cancer patients. We found that all three comorbidity indices were statistically significant in predicting mortality. No previous study has compared the three comorbidity indexes examined herein in a population of colon cancer patients though other populations of cancer patients have been used. In contrast to our study, Soares et al[33] compared the ability of the ACE-27 and the CCI to predict 6-month mortality among critically ill cancer patients and found that only the ACE-27 index was significantly associated with overall survival. Like the present study, these investigators also found that only those patients with severe comorbidity had a significantly increased risk of death. Consistent with our results, in a

study among older patients with head and neck cancer, Sanabria et al[34] found that increasing comorbidity by both the NIA/NCI and ACE-27 indexes were significantly associated with decreased survival.

The ACE-27 comorbidity index is comprehensive and accounts for disease severity when assessing the comorbidity burden in an individual. The NIA/NCI index is comprehensive, but disease severity is not taken into consideration. The CCI is not as comprehensive as the other two indices but does weight conditions based on comorbidity burden. It was somewhat surprising that all comorbidity indices in this study were significantly associated with death and that the hazard ratios were not substantially different given the differences in the three comorbidity indices. For studies specifically interested in the effect of comorbidity, we prefer the ACE-27 because it is comprehensive, accounts for disease severity, and is straightforward in its application. However, our results have shown all three indices were significantly associated with all-cause mortality. Based on our results, selection of any of the three comorbidity indices in future studies is justifiable as the conclusions reached were the same for all three comorbidity indices.

This study has a number of strengths. Our method of comorbidity assessment, comprehensive medical record review, has been shown to be superior to other methods of comorbidity assessment, namely, the use of administrative databases.[35, 36] Utilizing the complete medical record assures that, if comorbidity information was recorded anywhere in the patient's medical chart, it was captured as part of the comorbidity assessment for each patient. Using databases based on billing codes is problematic in two ways. One, utilizing only billing codes assures that some comorbidity information will be lost.[37]

Two, these codes are based on the discharge summary. In the current study, we were interested in comorbidity information before surgery, reflecting the participants' usual state of health, in predicting mortality. Complications that arise peri- or postoperatively could result in inaccurate comorbidity information that is not reflective of the patient's true comorbidity burden. Another asset of this study is the long interval of time for entry into the study and the extensive amount of follow up. Each study participant has the potential to be followed for a minimum of five years from the end of the accrual period to the termination date of the study. With this long follow up period, extensive survival time could accrue allowing the effects of comorbid conditions to be observed. These effects may be missed in studies of shorter duration.

There are some limitations associated with the current study. One limitation (that could also be an asset) is the 20+ year time period for entry into the study. In an effort to account for improvements in patient care that occurred during this time period, we adjusted for year of surgery in our analysis. The earliest period in our study (1981-1986) was associated with a higher risk of death than the years following. However, this relationship was not statistically significant when adjusted for other risk factors. Nonetheless, there may be differences in the probability of survival between patients that entered the study in the earlier periods compared to the later years that were not sufficiently accounted for by adjusting for year of surgery. Another limitation of the current study is the retrospective collection of comorbidity information. Because we were limited by the quantity and quality of information in the medical record, certain comorbid conditions may have been missed. The ideal method of collecting comorbid information is at the time of cancer diagnosis. A way to improve ascertainment of

comorbid medical conditions in older patients is by use of a comprehensive geriatric assessment (CGA) at the time of cancer diagnosis. CGA has the ability to identify previously unrecognized comorbid conditions.[38] Another weakness of the current study is that information on cause of death was not available for study participants. This information would have been useful in determining the impact of comorbidity on cancer-specific as well as non-cancer causes of death. Finally, only the primary author of the study (RH) collected comorbidity information. Having a second abstractor of comorbidity information may have decreased the likelihood that errors were made or information was missed in the collection of comorbidity data.

The results of this study advocate including comorbidity information in cancer research studies. The assessment of comorbidity will minimize its impact as a potential source of bias leading to more accurate estimates of effect and ultimately, better treatment for the cancer patient if clinical trials can demonstrate that patients with moderate or severe comorbidity can also benefit from treatment. In our study, all three comorbidity indices were associated with mortality. Further studies are needed in order to further substantiate our results or to establish whether one or more comorbidity indices more accurately reflect the true comorbidity burden in the cancer patient.

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Table 1. Characteristics of the study population (N = 496) and bivariate associations with all-cause mortality

Characteristics	Study Participants n (%)	Unadjusted HR (95% CI)	p
Status			
Alive	163 (32.9)		
Deceased	333 (67.1)		
Median Follow-up (in months)	58.2		
Mean age (± s.d.)	66.9 (12.2)	1.25[1] (1.14, 1.37)	
Sex			
Male	225 (45.4)	ref	
Female	271 (54.6)	1.08 (0.87, 1.34)	
Race			
Caucasian	303 (61.2)	ref	
African American	193 (38.9)	1.23 (0.99, 1.53)	
Surgery Date			0.08
1981-1986	76 (15.3)	ref	
1987-1991	96 (19.4)	0.67 (0.48, 0.94)	
1992-1996	133 (26.8)	0.69 (0.50, 0.95)	
1997-2002	191 (38.5)	0.75 (0.55, 1.02)	
Private Insurance			
Yes	334 (67.6)	ref	
No	160 (32.4)	1.26 (1.01, 1.58)	
Smoking Status			0.77
No	297 (59.9)	ref	
Former	117 (23.6)	0.91 (0.69, 1.19)	
Current	82 (16.5)	0.98 (0.73, 1.32)	
ACE-27 Comorbidity			< 0.001
None	98 (19.8)	ref	
Mild	184 (37.1)	0.81 (0.60, 1.11)	
Moderate	128 (25.8)	1.20 (0.87, 1.66)	
Severe	86 (17.3)	1.56 (1.11, 2.20)	

HR indicates hazard ratio; CI indicates confidence
[1]For each 10-year increase in age

Characteristics	Study Participants	Unadjusted HR (95% CI)	p
Charlson Score			0.003
0	252 (50.8)	ref	
1	133 (26.8)	1.01 (0.78, 1.32)	
≥ 2	111 (22.4)	1.58 (1.21, 2.05)	
NIA/NCI Comorbidity			0.02
0-1	150 (30.2)	ref	
2-3	189 (38.1)	0.85 (0.65, 1.11)	
4-5	113 (22.8)	1.00 (0.74, 1.35)	
≥ 6	44 (8.9)	1.56 (1.06, 2.29)	
Stage			< 0.001
1	91 (18.4)	ref	
2	169 (34.1)	1.43 (1.00, 2.05)	
3	137 (27.6)	2.48 (1.72, 3.58)	
4	99 (20.0)	9.37 (6.40, 13.71)	
Grade			
Low	398 (80.2)	ref	
High	98 (19.8)	1.70 (1.32, 2.20)	
BMI			<0.01
Underweight	24 (4.8)	1.81 (1.15, 2.83)	
Normal	199 (40.1)	ref	
Overweight	168 (33.9)	0.86 (0.67, 1.11)	
Obese	105 (21.2)	0.77 (0.57, 1.03)	
Obstruction			
No	349 (70.4)	ref	
Yes	147 (29.6)	1.98 (1.58, 2.48)	
Received Blood			
No	471 (95.0)	ref	
Yes	25 (5.0)	1.96 (1.26, 3.06)	

HR indicates hazard ratio; CI indicates confidence interval.

Table 2. The association of comorbidity indices with mortality

Variable	ACE-27		NIA/NCI Index		CCI	
		Adjusted[1] HR (95% C.I.)		Adjusted[1] HR (95% C.I.)		Adjusted[1] HR (95% C.I.)
Comorbidity Level						
	Not Severe	ref	< 6	ref	< 2	ref
	Severe	1.63 (1.24, 2.15)	≥ 6	1.83 (1.29, 2.61)	≥ 2	1.46 (1.14, 1.88)
Race						
Caucasian		ref		ref		ref
African American		1.34 (1.06, 1.68)		1.34 (1.07, 1.69)		1.36 (1.08, 1.71)
Stage	Stages I & II	ref		ref		ref
	Stage III	1.95 (1.50, 2.54)		2.06 (1.57, 2.69)		1.95 (1.49, 2.54)
	Stage IV	8.96 (6.60, 12.18)		8.66 (6.39, 11.73)		8.54 (6.30, 11.57)
Grade						
Low		ref		ref		ref
High		1.55 (1.19, 2.03)		1.66 (1.27, 2.16)		1.59 (1.22, 2.08)
BMI						
Underweight		1.54 (0.96, 2.45)		1.56 (0.98, 2.49)		1.54 (0.97, 2.46)
Normal		ref		ref		ref
Overweight/Obese		0.77 (0.61, 0.97)		0.80 (0.63, 1.00)		0.77 (0.61, 0.97)
Bowel Obstruction		1.51 (1.19, 1.91)		1.54 (1.21, 1.94)		1.52 (1.20, 1.93)

HR indicates hazard ratio; CI indicates confidence interval.
[1]Adjusted for the variables listed as well as age.

EFFECT OF COMORBIDITY AND BODY MASS INDEX ON COLON CANCER SURVIVAL OF AFRICAN AMERICAN AND CAUCASIAN PATIENTS

By

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Abstract

Background. There is a survival disparity between African Americans and Caucasians with colon cancer. The aims of the present study were to quantify the prognostic impact of comorbidity and body mass index (BMI) on survival and assess whether these two variables could account for the decreased survival among African Americans.

Methods. Patients (n = 496) who underwent surgery for colon cancer at The University of Alabama at Birmingham (UAB) Hospital from 1981-2002 were analyzed in this study. Hazard ratios (HR) with 95% confidence intervals (CI) were obtained by Cox proportional hazards models for the association of race, comorbidity, BMI, and covariates with mortality. The confounding influence of comorbidity and BMI for the increased risk of death associated with African American race was evaluated. Effect modification by race and tumor stage for the association of comorbidity and BMI with mortality was assessed.

Results. African Americans experienced an increased risk of death compared to Caucasians (HR=1.34; 95% CI, 1.06-1.68). The highest comorbidity burden was associated with an increased risk of all-cause mortality (HR = 1.63; 95% CI, 1.24-2.15). For BMI, being underweight increased the risk of death (HR = 1.54; 95% CI, 0.96-2.45) while being overweight/obese was protective (HR = 0.77; 95% CI, 0.61-0.97). The effect of comorbidity was seen among those with early stage tumors while the effect of BMI was confined to patients with advanced tumors.

Conclusions. Comorbidity and BMI impact survival following surgery for colon cancer. However, neither comorbidity nor BMI accounts for any of the excess mortality associated with African American race.

Introduction

In 2008, there will be an estimated 108,000 new cases of colon cancer and 50,000 deaths due to colorectal cancer (CRC) which ranks this cancer third in terms of incidence and mortality among men and women in the United States.[1] The public health impact of colon cancer has declined over the past 25 years as evidenced by a decreasing incidence as well as better survival due to earlier detection and improved treatment.[2-4] Despite these improvements, there continues to be a survival disparity among non-Hispanic African Americans and non-Hispanic Caucasians.[5-7] The 5-year survival rate of African Americans is less than that of Caucasians for nearly all cancers, including colon cancer.[1] In fact, the survival difference between African Americans and Caucasians has increased since the mid-1970s.[1] A variety of reasons have been postulated for the survival disparity between the races. Investigators have suggested that differences between African Americans and Caucasians in access to health-care, exposure to risk factors (e.g. obesity), stage at diagnosis, comorbidity, the physician-patient relationship, socioeconomic status, and tumor characteristics may explain the observed racial difference in survival.[1, 6, 8-11] However, the degree to which these factors operate in determining survival remains unclear.

Comorbidity is defined as the presence of other diseases in conjunction with an index disease (e.g. colon cancer) of primary interest.[12] The study of comorbidity is important because comorbid conditions in the cancer patient can impact the timing of cancer detection, treatment, prognosis, and outcome.[13] As others have speculated, comorbidity may be partly responsible for the decreased survival observed in African

Americans with colon cancer. Since comorbid conditions can exert their effects at multiple levels along the spectrum of care for the cancer patient, failure to account for comorbidity in cancer studies could result in confounding bias.[14] Thus, the increased risk of death among African Americans with colon cancer may be due to, at least in part, failing to account for comorbid conditions in statistical analyses.

The association between obesity and the risk of developing colon cancer has been the subject of numerous epidemiologic investigations.[15, 16] The consensus on this issue is that obesity increases the risk of getting colon cancer though the evidence is stronger for men than women. Despite the many studies that have focused on obesity and incident colon cancer, few have assessed the impact of body habitus and the relationship with survival following a diagnosis. In addition, no study has investigated the role of BMI as an explanation for the decreased survival observed among African Americans with colon cancer compared with Caucasians. Differences in body habitus between African Americans and Caucasians could possibly shed light on the issue of survival disparity between the races.

The aims of the present study were to assess the role of comorbidity and body habitus with survival following surgery for colon cancer in a patient population at one institution. In addition, we sought to investigate the potential confounding influence of comorbidity and BMI as an explanation for the decreased survival of African Americans with colon cancer relative to Caucasians. Last, we examined the impact of comorbidity and BMI by race and tumor stage in order to increase our understanding of how these risk factors determine survival within race and according to tumor status. The results of this study will contribute to a greater understanding of the role of comorbidity and BMI and

the association with survival following surgery for colon cancer. In addition, the results of the present study will allow insight into the survival disparity observed between African Americans and Caucasians with colon cancer.

Materials and Methods

Our study population consisted of patients who underwent surgery for sporadic (non-genetic) adenocarcinoma of the colon at The University of Alabama at Birmingham (UAB) Hospital from 1981-2002. The termination date for the accrual of follow up information ended June 1, 2008. The initial patient population was comprised of 631 participants. In order to be eligible for this study, the diagnosis of first primary colon cancer had to be the earliest diagnosis of any cancer in the patient (with the exception of non-melanoma skin cancer). Therefore, we excluded patients previously diagnosed with cancer (n = 63). We also excluded subjects with more than one primary tumor (n = 13) and those with unknown tumor grade (n = 3). As an aim of this study was to assess the effect of comorbidity on survival, and as the impact of comorbidity increases as one ages, we excluded patients who were less than 40 years of age (n = 22). By excluding patients less than 40, we also minimized the probability of the tumor having a genetic cause as these tumors tend to occur at younger ages compared to non-genetic tumors.[17] We removed from our study population those patients who died of complications following surgery by excluding subjects who survived less than one month after tumor resection (n = 21). We also excluded patients who were citizens of other countries or originally from other countries (n = 7). Finally, as BMI was a primary variable of interest in this study,

we excluded 6 participants with missing height information. After the above exclusions were made, our study sample consisted of 496 patients. This study was approved by the Institutional Review Board (IRB) at UAB.

Demographic, clinical, and patient information regarding age at time of surgery, gender, race, surgery date, insurance status, comorbidity, height and weight, smoking status, receipt of chemotherapy, and perioperative variables was obtained from medical records. Age was treated as a continuous variable. Year of surgery was categorized in 5-6 year intervals based on the distribution of patients from 1981-2002. Smoking information was recorded as current, former, or never smoked. Insurance status was recorded as whether or not the patient had private insurance coverage. Information pertaining to chemotherapy was ascertained and a dichotomized variable for receipt of any chemotherapeutic regimen was created. We obtained height and weight information at the time of surgery for each participant and also recorded whether or not the patient experienced any weight loss prior to the diagnosis of colon cancer. From the height and weight data, we calculated BMI $\left[BMI = \frac{weight\ (kg)}{height\ (m)^2}\right]$ and categorized each study participant as underweight (BMI < 18.5), normal weight (BMI: 18.5–24.9), overweight (BMI 25.0–29.9), and obese (BMI ≥ 30.0) according to WHO and NIH recommended cutpoints.[18, 19] The presence of bowel obstruction at the time of surgery and whether the participant received any blood transfusions during surgery was also recorded.

Tumor specific characteristics were obtained from pathology reports and adjudicated by two of the authors (CS, UM). Tumors were classified by the tumor-node-metastasis (TNM) system and staged according to the American Joint Committee on

Cancer (AJCC) staging system as Stages I, II, III, and IV.[20] Tumor grade was recorded as well differentiated, moderately differentiated, poorly differentiated, or unknown (there were no tumors that were graded as undifferentiated). As suggested by Compton et al,[21] well and moderately differentiated tumors were referred to as "low" grade, and poorly differentiated tumors were designated as "high" grade.

Comorbidity information was abstracted from the medical record up to the date of surgery by the primary author (RH). This data was obtained from several sources in the medical record including physician notes, anesthesia notes, nursing notes, and discharge summaries. Only comorbidities present before surgery were included in the comorbidity assessment. The Adult Comorbidity Evaluation-27 was used as the instrument of comorbidity assessment in this study as it was designed to assess the comorbidity burden specifically in patients with cancer.[22] Using the ACE-27, each study participant is given an overall grade of none, mild, moderate, or severe comorbidity as detailed by the Piccirillo et al.[22] As having a previous cancer was an exclusion criterion for this study, information pertaining to cancer was not used in the calculation of comorbidity burden.

Follow up data was obtained on each subject from the UAB tumor registry. This information is updated every 6 months for each patient by contacting the patient or a family member. If a patient has died since the last follow up contact, the date of death is recorded though cause of death is not obtained. Patients that were still alive at the termination date of the study are right censored at the last contact date. If a patient was recorded as alive and ≥ 3 years had elapsed since the last contact, the patient was designated as "lost to follow up."

Statistical Analysis

Survival time was calculated from the date of surgery until either death, the termination date of the study, or the last date of contact for patients that were still alive. The event of interest was death from any cause. All reported p values are two-sided, and statistical significance was defined as $P < 0.05$.

Chi-square (χ^2) statistics for categorical variables and t-tests for continuous variables were used to assess differences in vital status, demographic variables, comorbidity, tumor characteristics, chemotherapy status, and perioperative variables according to race. The Kaplan-Meier method was used compare the survival experience of African Americans and Caucasians with statistical significance determined by the log-rank test. The Cox proportional hazards (PH) model was used to obtain bivariate and adjusted hazard ratios (HR) with 95% confidence intervals (CI) for the association of risk factors and other covariates with mortality. From the bivariate analysis, each variable that obtained $P < 0.20$ was considered a potential confounder for the risk factors of interest in this study (race, comorbidity, BMI) and the association with all-cause mortality. For the multivariable model, potential confounders that met the above criterion were included in a model containing age, tumor stage, race, comorbidity, and BMI. The effect of age was fully characterized by the linear term and was not improved by the addition of quadratic or cubic terms. The final model was obtained by step-wise removal (the variable with the highest P value was removed and the model reanalyzed) of covariates that were no longer associated with mortality and therefore, not confounders.

The proportional hazards assumption was evaluated and met for race, comorbidity, and BMI in the multivariable model by testing the interaction between each variable with time. In addition, after obtaining the final model, the statistical significance of all two-way interactions between African American race, comorbidity, body habitus, and tumor stage was assessed. From the multivariable model, we also evaluated the confounding influence of comorbidity and BMI for the association of African American race with survival. Last, effect modification of comorbidity and BMI was assessed by race and tumor stage.

Results

Characteristics of the study population by race are shown in Table 1. The proportion of African Americans (39.2%) and Caucasians (60.8%) reflects the UAB Hospital's patient population. Significantly more African Americans were deceased at the end of follow up (74.1% v. 62.7%; $P < 0.01$). The median time of death for African Americans was over two years earlier (49.5 v. 76.1 months; $P = 0.06$) than that for Caucasians. There were more African American females (62.2 v. 49.8%; $P < 0.01$) while the gender distribution among Caucasians was uniform. More African Americans enrolled during the earlier years of the study period compared with Caucasians (1981-1991: 41.4 % v. 30.4%; $P = 0.03$). African Americans were also less likely to have private insurance (46.6% v. 81.1%; $P < 0.01$) and more likely to be non-smokers (66.3% v. 55.8%; $P = 0.04$). There was no difference in the mean age of African American and Caucasian study participants at the time of surgery.

Regarding comorbidity, African Americans were more likely to be in the severe category of comorbidity (22.8% v. 13.9%; P < 0.01). For BMI, proportionately more African Americans were underweight (8.3% v. 2.6%) and obese (28.5% v. 16.5%; P < 0.01) compared to Caucasians. There was no statistically significant difference between the races with regard to tumor stage at the time of surgery (P = 0.08) though African Americans were less likely to have high grade tumors (14.5% v. 23.1%; P = 0.02). African Americans were also less likely to receive chemotherapy (18.7% v. 32.3%; P < 0.01). There was no difference by race in participants who presented with bowel obstruction, received blood during surgery, or reported recent weight loss prior to surgery.

The risk factors that predicted survival in the multivariable model are shown in Table 2. Based on the results obtained from the unadjusted association of each risk factor with survival, we combined categories when the hazard ratios were similar. Therefore, we combined strata for comorbidity, BMI, and tumor stage. From the results obtained in the multivariable model, African Americans experienced a 34% increased risk of death that was statistically significant (HR= 1.34; 95% CI, 1.06-1.68). In addition, comparison of the adjusted and crude hazard ratios reveals negative confounding; the risk of death associated with African American race becomes stronger in magnitude and statistically significant after adjustment for other risk factors. For comorbidity, only those with the most severe comorbidity burden had an increased risk of death. Study participants with severe comorbidity at the time of surgery had a 63% increased risk of death due to any cause (HR= 1.63; 95% CI, 1.24-2.15). In the assessment of body habitus at the time of surgery, underweight patients were at increased risk of death (HR= 1.54; 95% CI, 0.96-

2.45) that was marginally statistically significant while overweight/obese participants had a decreased risk (HR= 0.77; 95% CI, 0.61-0.97). The likelihood ratio test was performed for the overall effect of BMI with death due to any cause. The addition of BMI significantly improved the survival model ($\chi^2_8 = 20.4$; $P < 0.01$). Stage was highly predictive of survival. Compared to those with stage I or II cancers, those with stage III disease experienced nearly a 2-fold increased risk of death (HR= 1.95; 95% CI, 1.50-2.45) and those with metastatic disease had nearly a 9-fold increase in risk (HR= 8.96; 95% CI, 6.60-12.18). High tumor grade was associated with a 55% increased risk (HR= 1.55; 95% CI, 1.19-2.03) and the presence of bowel obstruction increased the risk of death by 51% (HR= 1.51; 95% CI, 1.19-1.91). Year of surgery (1981-86 v. 1987-2002: HR = 1.42; 95% CI, 1.09-1.85), lack of private insurance (HR= 1.26; 95% CI, 1.01-1.58), receipt of chemotherapy (HR= 1.72; 95% CI, 1.36-2.16), receiving blood during surgery (HR= 1.95; 95% CI, 1.25-3.03), and recent weight loss (HR= 1.52; 95% CI, 1.22-1.90) were all associated with mortality in the unadjusted analysis. However, none of these covariates remained statistically significant in the multivariable model. In addition, no interaction terms were statistically significant though we were not sufficiently powered to detect interactions of the magnitude expected in our study.

Table 3 displays the association of African American race with survival in five models: the crude association, in a model adjusted for stage only, a model adjusted for all risk factors other than comorbidity, a model adjusted for all risk factors other than BMI, and the fully adjusted model. The purpose of this table is to evaluate the confounding influence of stage, comorbidity, and BMI in the association of African American race with survival. Comparing the HR obtained for the crude association of African American

race with survival and the other HRs shown in the table, we see that only stage is a confounder of the race relationship with survival. We can assess whether there is confounding by comorbidity and/or BMI by comparing the HRs obtained for the fully adjusted models without these variables shown in the two columns of Table 3 to the fully adjusted HR depicted in the last column. If a substantial shift toward the null for the HR associated with African American race occurred after adjustment for either of these variables, we could conclude that one or both of these variables do, in fact, explain some of the excess risk of death associated with African American race. That is, failure to account for the confounding influence of comorbidity and/or BMI in previous studies explains a portion of the increased risk of death for African Americans. However, there was no meaningful change in the HR associated with African American race after adjustment for either comorbidity or BMI. We conclude from our study that neither comorbidity nor BMI is a confounder of the association of race with death and thus, comorbidity and BMI do not explain any of the increased risk of all-cause mortality observed for African Americans.

Table 4 displays the association of comorbidity and BMI stratified by race. Comparing the effect of comorbidity by race, for African Americans, those with severe comorbidity had an 83% increased risk of death (HR= 1.82; 95% CI, 1.22-2.70) that was statistically significant. Caucasians also had an increased risk of death for those with severe comorbidity though the association was smaller in magnitude (HR= 1.49; 95% CI, 0.99-2.23) and borderline statistically significant. In evaluating the association of BMI with death, we were limited in our ability to assess the statistical significance for the association of underweight with survival by race due to small numbers in this category

(African Americans, n = 16: Caucasians, n = 8). However, there was an association between being underweight and increased risk of death for both African Americans and Caucasians. For African Americans, being underweight conferred a 40% (HR= 1.40; 95% CI, 0.78-2.52) increased risk of death while for Caucasians the risk was over 2-fold (HR= 2.16; 95% CI, 0.92-5.07). The protective effect of being overweight/obese was equivalent between the races.

The assessment of effect modification by tumor stage for the association of comorbidity and BMI is shown in Table 5. For the evaluation of effect modification by tumor stage, stages I & II were combined due to similar hazards of death as was done in previous models. Following this line of reasoning, stage III and stage IV were analyzed separately as those with metastatic disease were at substantially higher risk of death. For comorbidity, comparing the ratio measures obtained for stages I & II to those for stage III & stage IV illustrates the greater impact of comorbidity for those with less advanced disease. In addition, both moderate and severe comorbidity are associated with an increased risk of death for those with less advanced tumors. For stages I & II, moderate comorbidity increased the risk of death by 74% (HR= 1.74; 95% CI, 1.14-2.65), and those with severe comorbidity had over a 2-fold increased risk (HR= 2.22; 95% CI, 1.44-3.43). For those with stage III tumors, comorbidity was not associated with survival. For participants with metastatic colon cancer, there was an increased risk of death associated with moderate and severe comorbidity though this was not statistically significant. For BMI, there was no association with death for those with stage I & II tumors. Again, the ability to detect a statistically significant association between underweight and survival was limited due to a small numbers. Nonetheless, there was an association for those with

stage III tumors. Being underweight was associated with an 87% increased risk of death compared to normal weight individuals (HR= 1.87; 95% CI, 0.95-3.69) though this result was not statistically significant. The protective effect of being overweight/obese was confined to those with stage IV, metastatic disease. For participants with stage IV disease, being overweight/obese decreased the risk of death by 42% compared to those of normal weight (HR= 0.58; 95% CI, 0.37-0.90).

Discussion

A number of reasons have been put forth to explain the increased mortality of African Americans relative to Caucasians. The goals of this study were to quantify the overall effect of comorbidity and BMI on survival among a population of colon cancer patients, determine whether the decreased survival among African Americans relative to Caucasians is due to the confounding influence of comorbidity and/or BMI, and last, assess effect modification for the impact of comorbidity and BMI by race and tumor stage. In the present study, those with the highest comorbidity burden had an increased risk of death from any cause. The prognostic impact of comorbidity was confined to those with stage I or II tumors. In addition, being underweight was associated with an increased risk of death for those with stage III disease, and being overweight or obese was associated with a decreased risk for those with metastatic disease. Both comorbidity and BMI were associated with survival for African Americans and Caucasians. Though there appeared to be a greater detrimental effect for being underweight in Caucasians, caution must be used in interpreting the effect of underweight by race due to small

numbers in this category. Finally, the only confounder for the association of race with survival was tumor stage. Adjustment for comorbidity and BMI did not explain any of the increased mortality for African American colon cancer patients.

Only the developers of the ACE-27 index have used this index of comorbidity assessment in a population of colon cancer patients.[22, 23] In the study by Piccirillo et al,[22] increasing comorbidity was associated with decreased overall survival for all digestive system tumors. In the present study, only those with severe comorbidity had an increased risk of death, as shown in other populations of cancer patients.[24, 25] There was also effect modification by tumor stage. For those with stage I & II tumors, increasing comorbidity was associated with an increased risk of death. In contrast, for those with stage III and IV tumors, comorbidity was not associated with survival. Thus, with increasing stage, the cancer becomes the primary determinant of survival. This result is consistent with those reported by Read et al[23] for colon, breast, and prostate cancer.

Several investigators have adjusted for comorbidity in studies addressing the survival disparity between African Americans relative to Caucasians with colon or colorectal cancer. Cooper et al[26] compared the odds of death 2 years after surgery among Medicare beneficiaries and found that the increased risk of death among African Americans persisted after adjustment for gender, age, comorbidity, and tumor characteristics. Limitations of this study were the use of administrative data (discharge diagnoses in Medicare Provider Analysis and Review files) to ascertain comorbidity burden, the lack of a validated instrument for comorbidity assessment, and failure to account for survival time in the analysis. Using the Surveillance, Epidemiology, and End Results-Medicare linked database, Schrag et al[27] found an increased risk of death due to

any cause for African American race after adjustment for comorbidity and other covariates among stage II colon cancer patients. The comorbidity instrument used in this study was the Romano adaptation of the Charlson Comorbidity Index (CCI).[28]

Roetzheim et al[29] conducted a study to assess the effects of health insurance and race with survival following a diagnosis of colon cancer using the Florida Cancer Data System. The method of comorbiditiy assessment in this study was a variation of the CCI adapted for administrative databases.[30] These investigators also found an increased risk of overall mortality among African Americans after adjustment for comorbidity, demographic characteristics, insurance provider, measures of SES, tumor characteristics, and treatment. An acknowledged limitation of this study was incomplete comorbidity ascertainment and lack of information on disease severity due to the use of administrative data.

Two studies have addressed the issue of racial disparity among participants in the Veterans Affairs (VA) health-care system. Utilizing the Charlson Index, Rabeneck et al[31] analyzed all CRC patients who underwent surgery from October 1990 to September 2000. After adjustment for comorbidity and other risk factors, African American race was associated with an increased risk of mortality though the magnitude of association was smaller than has been reported in other studies. Dominitz et al[32] also used VA data and measured comorbidity burden with the CCI. African Americans had a modest though statistically significant increased risk of mortality after adjustment for comorbidity and other risk factors. A major limitation of both VA studies was lack of information on tumor stage and the acknowledged difficulty of ascertaining comorbid disease burden when utilizing administrative data.

Though the above studies demonstrated an increased risk of death for African Americans after adjustment for comorbidity, they did not address the question of whether comorbidity accounted for any of the excess risk. This question was addressed by Mayberry et al[7] as part of the National Cancer Institute Black/White Cancer Survival Study. These authors found an increased risk of death due to colon cancer and all causes among African Americans though the latter was not statistically significant. After adjustment for stage, the increased risk of colon cancer-specific death associated with African American race decreased by 60%. The addition of comorbidity did not result in a further reduction of the hazard ratio associated with African Americans. Furthermore, the addition of sociodemographic measures, tumor-related variables, symptoms of colon cancer (obstruction), health behaviors, and treatment also did not change the risk of mortality for African Americans. Strengths of this study were the use of in-person interviews and medical records to obtain information on study participants. However, it was unclear how comorbidity was defined.

As was the case in the study by Mayberry et al,[7] stage has been shown to be the primary determinant of survival differences by race.[10] However, our results were surprising because stage was actually a negative confounder of the association with African American race. This result can be explained by the fact that, though there were no statistically significant differences in stage at diagnosis between African Americans and Caucasians in our study, considerably more Caucasians (22.3% v. 16.8) were diagnosed with metastatic disease. This could account increase in magnitude of association for African American race that also became statistically significant after adjustment for tumor stage.

Only one other study by Gomez et al[33] has investigated the confounding influence of comorbidity in an attempt to unravel the racial differences in survival for patients with colon cancer. These authors found that comorbidity did not account for the increased risk of overall or colon cancer-specific mortality observed for African Americans. The CCI was utilized for comorbidity assessment and these investigators speculated that this index may not be comprehensive enough to detect differences in comorbidity between the races. In the current study, the ACE-27 comorbidity index was utilized as the method of comorbidity assessment with the idea that this index may be a more refined measure of comorbidity assessment than the CCI. This index is comprehensive and accounts for disease severity in quantifying the comorbidity burden among cancer patients. Despite this rationale guiding our decision to use the ACE-27 in our study, we reached the same conclusions as the previous two studies.[7, 33] Namely, comorbidity did not explain any of the increased risk of mortality for African Americans with colon cancer observed during the follow up period in our study.

The BMI component of this study was added to contribute to the few studies in the literature on this subject, to address the limitations of previous studies, and to assess the possible confounding influence of BMI for the association of African American race with mortality. When viewed in the context of tumor stage, the increased risk for underweight and the decreased risk for overweight/obese participants are biologically plausible and relate to the notion of frailty. A number of criteria can be used to identify the frail elderly including malnutrition and the presence of significant comorbidity.[34, 35] In our study, most patients that were underweight were older (mean age: 75.7 years) had either moderate or severe comorbidity (66.7%). Being underweight can be seen as a

marker of decreased biological reserve, and thus, decreased ability to compensate for the physical demands imposed by the cancer. Following the same line of reasoning, being overweight/obese can be seen as advantageous for individuals with metastatic disease. Having extra weight (biological reserve) in this scenario translates to a better ability to withstand the symptoms associated with a cancer of this advanced stage.

The results obtained for BMI in this study can be seen in the context of what other investigators have reported. Our results are consistent with the increased risk associated with underweight but are at odds with studies that also found an increased risk for obese individuals. The earliest study of BMI and survival following a diagnosis of colon cancer was conducted by Slatttery et al[36] using patients from the Utah Cancer Registry. These investigators found that BMI was not a significant predictor of survival. A weakness of this study was the fact that standardized cut-points for BMI were not used. Meyerhardt et al[37] reported that, among men and women with stage II & III colon cancer enrolled in a clinical trial, underweight men experienced an increased risk of overall mortality though for women, obesity was associated with an increased risk of death. As part of the National Surgical Adjuvant Breast and Bowel Project (NSABP), Dignam et al[38] reported that, among patients with Dukes B and C colon cancer, underweight participants were at increased risk of non-colon cancer-related deaths and very obese participants were at increased risk of death due to colon cancer. Doria-Rose et al[39] conducted a study to assess the effect of BMI on survival following colon cancer diagnosis among post-menopausal women in Wisconsin. An increased risk of death due to colon cancer was found among both underweight and overweight women. Last, in an Australian study by Haydon et al,[40] BMI was not associated with overall or disease-specific survival though

other measures of obesity were associated with an increased risk of death. No association with underweight was investigated in this study as both underweight and normal weight participants served as the referent group. To our knowledge, the current study is the first that has investigated body habitus in an effort to explain the increased risk of death for African Americans with colon cancer.

The present study has a number of strengths. Our method of comorbidity assessment, comprehensive medical record review, has been shown to be superior to other methods of comorbidity assessment, namely, the use of administrative data.[41] Utilizing the complete medical record assures that if comorbidity information was recorded anywhere in the patient's medical chart, it was captured as part of the comorbidity assessment for each patient. Using databases based on billing codes is problematic in two ways in the current study. One, utilizing billing codes almost assures that some comorbidity information will be lost. Two, these codes are based on the discharge summary. In the current study, we were interested in comorbidity information before surgery, reflecting the participants' usual state of health, in predicting survival. Complications that arise peri- or postoperatively could result in inaccurate comorbidity information that is not reflective of the patient's true comorbidity burden. Another asset of this study is long interval of time for entry into the study and the extensive amount of follow up. Each study participant has the potential to be followed for a minimum of over five years from the end of the accrual period to the termination date of the study. With this long follow-up period, extensive survival time could accrue allowing the effects of comorbid conditions to be observed which may be missed in studies of shorter duration.

There are some limitations of the current study that should be considered. One limitation (that could also be an asset) is the 20+ year time period for entry into the study. In an effort to adjust for improvements in patient care that occurred during this time period, we adjusted for year of surgery in our analysis. The earliest period in our study (1981-1986) was associated with a higher risk of death than the years following. However, this relationship was not statistically significant when adjusted for other risk factors. Nonetheless, there may be differences in the probability of survival between patients that entered the study in the earlier periods compared to the later years that were not sufficiently accounted for by adjusting for year of surgery. Another limitation of the current study is the retrospective collection of comorbidity information. As we were limited by the quantity and quality of information in the medical record, certain comorbid conditions may have been missed. The ideal method of collecting comorbid information is at the time of cancer diagnosis. Another weakness is that information on cause of death was not available for study participants. This information would have been useful in determining the impact of comorbidity and BMI on cancer-specific as well as non-cancer causes of death. Finally, only the primary author of the study (RH) collected comorbidity information. Having a second abstractor of comorbidity information may have decreased the likelihood that errors were made in the collection of comorbidity data.

The issue of racial disparity in survival among patients with cancer is likely multifactorial and has been attributed to a number of causes. Though the current study has shown that comorbidity and BMI are associated with all-cause mortality in patients with colon cancer, the results presented herein as well as previous investigations suggest that comorbidity and BMI are not likely to explain the decreased survival associated with

African American race. There is evidence from VA studies which support the idea that when access to treatment is equivalent, the racial disparity in survival is greatly reduced.[31, 32] However, whether the survival difference is diminished due to equal access to the medical system or due to similarity of socioeconomic background or other potential confounders among this population is a matter of speculation.[42] As socioeconomic and sociodemographic variables are often unavailable or inadequately measured, differences in these variables between African Americans and Caucasians may be responsible for observed survival differences by race in colon cancer as well as other chronic diseases. Further investigation is needed to gain a greater understanding of this complex issue so that efforts can be directed toward the primary cause of mortality differences by race.

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Table 1. Characteristics of the study population

Characteristics	African-American n (%)	Caucasian n (%)	P
	193 (39.2)	**303 (60.8)**	—
Status			< 0.01
Deceased	143 (74.1)	190 (62.7)	
Median Overall Survival (in months)	49.5	76.1	0.06
Mean age at surgery (± s.d.)	67.2 (11.8)	66.6 (12.5)	0.60
Sex			< 0.01
Male	73 (37.8)	152 (50.2)	
Female	120 (62.2)	151 (49.8)	
Surgery Date			0.03
1981-1986	40 (20.7)	36 (11.9)	
1987-1991	40 (20.7)	56 (18.5)	
1992-1996	50 (25.9)	83 (27.4)	
1997-2002	63 (32.6)	128 (42.2)	
Private Insurance			< 0.01
Yes	90 (46.6)	244 (81.1)	
Smoking Status			0.04
Non-smoker	128 (66.3)	169 (55.8)	
Former	35 (18.1)	82 (27.1)	
Current	30 (15.5)	52 (17.2)	
ACE-27 Comorbidity			< 0.01
None	25 (13.0)	73 (24.1)	
Mild	69 (35.8)	115 (38.0)	
Moderate	55 (28.5)	73 (24.1)	
Severe	44 (22.8)	42 (13.9)	
BMI			< 0.01
Underweight	16 (8.3)	8 (2.6)	
Normal	70 (36.3)	129 (42.6)	
Overweight	52 (26.9)	116 (38.3)	
Obese	55 (28.5)	50 (16.5)	

Characteristics	African-American n (%)	Caucasian n (%)	P
Tumor Stage			0.08
1	34 (17.6)	57 (18.8)	
2	63 (32.6)	106 (35.0)	
3	65 (33.7)	72 (23.8)	
4	31 (16.1)	68 (22.4)	
Tumor Grade			0.02
High	28 (14.5)	70 (23.1)	
Low	165 (85.5)	233 (76.9)	
Chemotherapy			< 0.01
Yes	36 (18.7)	98 (32.3)	
Obstruction			0.57
Yes	60 (31.1)	87 (28.7)	
Received Blood			0.91
Yes	10 (5.2)	15 (5.0)	
Recent weight loss			0.18
Yes	69 (35.8)	91 (30.0)	

Table 2. Bivariate and adjusted associations with death

	Hazard Ratios	
Variable	**Unadjusted (95% C.I.)**	**Adjusted[1] (95%C.I.)**
Race		
Caucasian	ref	ref
African American	1.23 (0.99, 1.53)	1.34 (1.06, 1.68)
ACE-27 Comorbidity		
Not Severe	ref	ref
Severe	1.62 (1.24, 2.11)	1.63 (1.24, 2.15)
BMI		
Underweight	1.81 (1.15, 2.83)	1.54 (0.96, 2.45)
Normal	ref	ref
Overweight/Obese	0.83 (0.66, 1.03)	0.77 (0.61, 0.97)
Tumor Stage		
Stages I & II	ref	
Stage III	1.96 (1.51, 2.54)	1.95 (1.50, 2.54)
Stage IV	7.38 (5.55, 9.79)	8.96 (6.60, 12.18)
Tumor Grade		
Low	ref	ref
High	1.70 (1.32, 2.20)	1.55 (1.19, 2.03)
Bowel Obstruction	1.98 (1.58, 2.48)	1.51 (1.19, 1.91)

HR indicates hazard ratio; CI indicates confidence
[1]Adjusted for the variables listed as well as age.

Table 3. The association of African American race with all-cause mortality

	Hazard Ratios with 95% CI				
Variable	**Unadjusted**	**Adjusted for Stage**	**Fully Adjusted[1] minus comorbidity**	**Fully Adjusted[1] minus BMI**	**Fully Adjusted[1]**
Race					
Caucasian	ref	ref	ref	ref	ref
African American	1.23 (0.99, 1.53)	1.37 (1.10, 1.71)	1.36 (1.08, 1.71)	1.38 (1.10, 1.73)	1.34 (1.06, 1.68)

CI indicates confidence interval.
[1]The fully adjusted model is adjusted for age, race, comorbidity, BMI, tumor stage, tumor grade, and bowel obstruction.

Table 4. The association of comorbidity and BMI with death by race

	African Americans		Caucasians	
	HR[1]	**(95% C.I.)**	**HR[1]**	**(95% C.I.)**
ACE-27 Comorbidity				
Not Severe	ref		ref	
Severe	1.82	(1.22, 2.70)	1.49	(0.99, 2.23)
BMI				
Underweight	1.40	(0.78, 2.52)	2.16	(0.92, 5.07)
Normal	ref		ref	
Overweight/Obese	0.77	(0.53, 1.13)	0.78	(0.58, 1.06)

HR indicates hazard ratio; CI indicates confidence interval.
[1]Hazard Ratios adjusted for age, comorbidity, BMI, tumor stage, tumor grade, and bowel obstruction.

Table 5. The association of comorbidity and BMI with death by tumor stage

	Stages I & II	Stage III	Stage IV
	HR[1] (95% C.I.)	**HR[1] (95% C.I.)**	**HR[1] (95% C.I.)**
ACE-27 Comorbidity			
None/Mild	ref	ref	ref
Moderate	1.74 (1.14, 2.65)	0.99 (0.85, 1.68)	1.25 (0.77, 2.02)
Severe	2.22 (1.44, 3.43)	1.16 (0.78, 1.74)	1.80 (0.87, 3.72)
	Stages I & II	**Stage III**	**Stage IV**
	HR[1] (95% C.I.)	**HR[1] (95% C.I.)**	**HR[1] (95% C.I.)**
BMI			
Underweight	1.07 (0.50, 2.27)	1.87 (0.95, 3.69)	1.28 (0.16, 10.04)
Normal	ref	ref	ref
Overweight/Obese	0.92 (0.65, 1.30)	0.92 (0.59, 1.45)	0.58 (0.37, 0.90)

HR indicates hazard ratio; CI indicates confidence interval.
[1]Hazard Ratios adjusted for age, race, comorbidity, BMI, tumor grade, and bowel obstruction.

CONCLUSIONS

African Americans have lower survival rates for nearly all forms of cancer including colon cancer. Africans Americans are also more likely to be diagnosed with more advanced colon tumors compared to Caucasians which accounts for some of the increased risk of death following a diagnosis. However, African Americans still have worse survival when survival rates are compared between the races within stage. Several factors have been proposed to explain the disparity in survival. Among the reasons put forth to explain the increased risk of death in African Americans are comorbidity and body habitus. This study measured the comorbidity burden and body disposition of a population of colon cancer patients at one institution in an effort to find out if one or both could account for the increased risk of death in African Americans.

Before answering the question regarding the effect of comorbidity and body habitus as it relates to the issue of racial disparity, the prognostic value of three comorbidity indices was evaluated, and the results obtained for the three indices were compared. The three comorbidity indices evaluated were: the Adult Comorbidity Evaluation-27 (ACE-27), the National Institute on Aging and National Cancer Institute (NIA/NCI) Comorbidity Index, and the Charlson Comorbidity Index (CCI). The ACE-27 comorbidity index is a relatively new comorbidity index designed specifically for cancer patients that contains 27 relevant comorbid conditions which are graded as mild, moderate, or severe based on organ decompensation. Study participants are given an overall score (0 = none, 1 = mild, 2 = moderate, 3 = severe) corresponding to total

comorbidity burden. The NIA/NCI comorbidity index is a comprehensive listing of comorbid conditions falling under 27 categories. Total comorbidity count is obtained for each participant by a simple counting of comorbid conditions. The CCI is by far the most popular comorbidity index and consists of 19 comorbid conditions. Each comorbid disease is weighted and study subjects are given a total score. In reference to the first paper of this dissertation, for all three comorbidity indicies, only the most severe category of comorbidity was associated with death due to any cause. The risk estimates associated with the most severe category of comorbidity were also similar for the three indicies. For the ACE-27, those in the most severe category of comorbidity experienced a 63% increased risk of death (ACE-27: HR = 1.63; 95% CI, 1.24–2.15). For the NIA/NCI comorbidity index, those with the highest comorbidity burden (≥ 6) experienced an 83% increased risk of death (HR = 1.83; 95% CI, 1.29–2.61). Finally, an increased risk of death due to any cause was found for those with a CCI score ≥ 2 (HR = 1.46; 95% CI, 1.14–1.88) though the magnitude of association was smaller compared to the other two indicies. Another important finding is that the results obtained for other risk factors and potential confounders were nearly identical across all three models. In conclusion, strikingly similar results were obtained in a survival model with death as the outcome regardless of the measure of comorbidity used. For future cancer research studies, the decision to use a particular comorbidity index should be guided by the goals of the study, the data available to the investigator, and the resources necessary to acquire the data.

The implications regarding this aspect of the dissertation concern both past and future cancer research studies. This aspect of the dissertation gives investigators assurance of the comparability of results obtained using different comorbidity indices in

studies of cancer. For future cancer studies in which comorbidity *per se* is not of primary interest, good research practice dictates that comorbidity should be accounted for in the statistical analysis as comorbidity may operate as a confounder of the variables of primary interest. As has been shown, selection of one of the three comorbidity indices examined in the present study is justified. It is to be emphasized that an assessment of comorbidity is an important aspect of studies investigating cancer outcomes. It is that comorbidity assessment is performed in cancer research studies, not the index of comorbidity that is chosen which is of primary importance. In addition, incorporation of comorbidity assessment into clinical trials research would allow for more accurate estimates of treatment-related toxicity, drug-drug interactions, and efficacy of a particular therapeutic regimen.[48, 49]

The pivotal question that this dissertation study sought to address was whether or not comorbidity and/or BMI could explain the survival disparity between African Americans and Caucasians following surgery for colon cancer. The index of comorbidity used in the second paper was the ACE-27 index. As reported, those with severe comorbidity experienced an increased risk of death due to any cause. The prognostic effect of comorbidity was confined to those with stage I or II tumors (HR_{mod} = 1.74; 95% CI, 1.14-2.65: HR_{severe} = 2.22; 95% CI, 1.44-3.43). In addition, being underweight was associated with an increased risk of death for those with stage III disease (HR= 1.87; 95% CI, 0.95-3.69) though this result was not statistically significant. Study participants with stage IV disease who were overweight or obese had a decreased risk of death (HR= 0.58; 95% CI, 0.37-0.90). Both comorbidity and BMI were associated with mortality for African Americans and Caucasians (see Table 4, page 64). Though there appeared to be

a greater detrimental effect for being underweight in Caucasians, caution must be used in interpreting the effect of underweight by race due to small numbers in this category. Finally, the only confounder for the association of race with survival was tumor stage. Adjustment for comorbidity and BMI did not explain any of the increased mortality for African American colon cancer patients.

The answer to the question of what accounts for the poorer survival observed in African Americans with colon cancer relative to their Caucasian counterparts has remained elusive. The present study sought to examine two factors, comorbidty and body habitus, which some investigators have proposed as possible reasons for the survival disparity between the races. In the present study, neither comorbidity nor body habitus could account for the increased risk of death observed for African Americans. This study was the first study to examine the effect of body habitus as an explanation for the survival disparity by race in colon cancer. This study sought to address the potential limitations of the previous two studies[10, 50] that examined the confounding influence of comorbidity and the association of race with mortality in colon cancer patients. The fact that neither comorbidity nor BMI accounted for any of the increased risk of death seen in African Americans in the present study has implications for future research aimed at addressing this issue. Clues from Veterans Affairs (VA) studies that have reported a much lower disparity in survival between African Americans and Caucasians are instructive. As noted previously, whether the decreased risk observed in these two VA studies is due to equal treatment or similarity in socioeconomic/sociodemographic background is uncertain.[51] Insight into the issue of racial disparity and survival among colon cancer patients may be gained in future studies that focus on the confounding

influence of treatment and socioeconomic/sociodemographic measures. Answering the question of what accounts for the racial disparity in survival following surgery for colon cancer is important so that efforts can be aimed at addressing the cause of poorer survival in African Americans. Addressing health disparities is a goal of public health and one that is necessary to ensure that all Americans have the opportunity to lead healthy lives.

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APPENDIX A
IRB APPROVAL

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Institutional Review Board for Human Use

Form 4: IRB Approval Form
Identification and Certification of Research
Projects Involving Human Subjects

UAB's Institutional Review Boards for Human Use (IRBs) have an approved Federalwide Assurance with the Office for Human Research Protections (OHRP). The UAB IRBs are also in compliance with 21 CFR Parts 50 and 56 and ICH GCP Guidelines. The Assurance became effective on November 24, 2003 and expires on September 19, 2010. The Assurance number is FWA00005960.

Principal Investigator: HINES, ROBERT BROOKS

Co-Investigator(s):

Protocol Number: **X071218008**

Protocol Title: *Comorbidity and Body Mass Index (BMI) as Predictors of Survival for African Americans and Caucasians Following Surgery for Adenocarcinoma of the Colon*

The IRB reviewed and approved the above named project on 1-08-08. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.

IRB Approval Date: 1-08-08

Date IRB Approval Issued: 1-08-08

HIPAA Waiver Approved?: Yes

Marilyn Doss

Marilyn Doss, M.A.
Vice Chair of the Institutional Review Board for Human Use (IRB)

Investigators please note:

The IRB approved consent form used in the study must contain the IRB approval date and expiration date.

IRB approval is given for one year unless otherwise noted. For projects subject to annual review research activities may not continue past the one year anniversary of the IRB approval date.

Any modifications in the study methodology, protocol and/or consent form must be submitted for review and approval to the IRB prior to implementation.

Adverse Events and/or unanticipated risks to subjects or others at UAB or other participating institutions must be reported promptly to the IRB.

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Principal Investigator:	HINES, ROBERT BROOKS
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Protocol Number:	**X071218008**
Protocol Title:	*Comorbidity and Body Mass Index (BMI) as Predictors of Survival for African Americans and Caucasians Following Surgery for Adenocarcinoma of the Colon*

The IRB reviewed and approved the above named project on 11-25-08. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services. This Project will be subject to Annual continuing review as provided in that Assurance.

This project received EXPEDITED review.

IRB Approval Date: 11-25-08

Date IRB Approval Issued: 11-25-08

HIPAA Waiver Approved?: Yes

Marilyn Doss

Marilyn Doss, M.A.
Vice Chair of the Institutional Review Board for Human Use (IRB)

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