



WOMEN'S FOUNDATION

## ***Understanding the Consequences of Co-Existing Medical Conditions Among Women Diagnosed with Breast Cancer in Missouri***

Commissioned by Women's Foundation with funding support from Missouri Foundation for Health

Kala Visvanathan MD, MHS and Avonne Connor PhD, MPH,  
Johns Hopkins Bloomberg School of Public Health

### ***EXECUTIVE SUMMARY:***

Missouri has high rates of mortality from female breast cancer <sup>1</sup> as well as other chronic diseases such as type 2 diabetes<sup>2</sup>, cardiovascular disease, hypertension<sup>3</sup>, and kidney disease <sup>1</sup>. There is growing evidence that women with co-existing conditions – or comorbidities – at the time of their breast cancer diagnosis may have a worse prognosis. These conditions in women with breast cancer may also explain the high mortality rates among vulnerable populations such as those with low household incomes, those living in rural/underserved areas, as well as African Americans and the elderly. Understanding how these conditions impact mortality rates can provide patients, providers and policymakers with valuable insights into how to improve the overall health of women with breast cancer and increase longevity.

To better understand how common coexisting medical conditions affect the mortality of women diagnosed with breast cancer at the population level in Missouri, the Women's Foundation commissioned a first-of-its-kind study, bringing together a team of experienced population-based scientists and clinicians from Johns Hopkins Bloomberg School of Public Health, Johns Hopkins School of Medicine, and the University of Missouri, which is home to the Missouri Cancer Registry and Research Center.

With a data set that included 36,581 Missouri women diagnosed with invasive breast cancer obtained from the cancer registry and hospital discharge data across the state, researchers identified the top three co-existing medical conditions: essential hypertension, cardiovascular diseases (CVD), and type 2 diabetes. A comorbidity "score" was also developed to look for differences in survival based on the number of co-existing conditions present at the time of diagnosis. This study benefited from a large sample and high-quality data representing the entire state over many years.

These results provide a window of opportunity for patients, providers, and policymakers to improve the overall health of women with breast cancer through closer monitoring and better management of their chronic diseases. They also send a strong message to cancer free women and their providers regarding the importance of maintaining good health throughout their lives.

### **Some Key Findings:**

- The three most prevalent non-cancer conditions identified at the time of breast cancer diagnosis were type 2 diabetes, essential hypertension, and CVD. Notably, 46% of women with breast cancer had at least one of the three co-existing conditions. The prevalence of these conditions was higher among African American women with over half of them having at least one.

- A higher percentage of women living in neighborhoods with >20% of the poverty level were burdened by 2 or more co-existing conditions (20.5%) compared to breast cancer patients living in neighborhoods with <5% of the national poverty level (11.1%).
- There were differences in mortality based on the presence of co-existing conditions by age, race, and poverty. African American women with CVD had a two-fold risk of all-cause mortality.
- Women living in large urban areas with all three co-existing conditions were more than three times more likely to die of any cause. Women with an increased poverty score also had higher mortality.
- Researchers found an increase in breast cancer-specific mortality among women with co-existing conditions, supporting the hypothesis that these conditions may also contribute to disease progression of their cancer. Specifically, women with two co-existing conditions had a 30% increase in breast cancer mortality and with three co-existing conditions a 57% increase in breast cancer mortality.
- Researchers found that the number of hospitalizations was a strong predictor of survival among BC survivors with coexisting conditions. Breast cancer patients with five or more hospitalizations had over a 300% increase in risk of death compared to those without hospitalizations. **Breast cancer patients with all three co-existing conditions had over a 200% increase in risk of death compared to those without these three comorbidities (HR, 2.41; 95% CI 2.21-2.63).** Approximately 23% of African American women who experienced a hospitalization had at least one of three co-existing conditions (diabetes, HBP, or CVD) (Figure 5). Women with all three co-existing conditions were over three times more likely to ever be hospitalized compared to women without diabetes, HBP, and CVD (Figure 6).

### Policy Implications

- These results provide strong evidence that co-existing conditions such as CVD, diabetes and hypertension play a major role in the mortality of breast cancer patients in the state of Missouri.
- Evaluation, treatment and monitoring of co-existing conditions at the time of breast cancer diagnosis has the potential to improve survival, particularly in vulnerable populations. This could have significant public health impact given the prevalence of breast cancer.
- Frequency of hospitalizations may be a good indicator of the impact of co-existing conditions among breast cancer survivors.
- The public health impact could be even greater through the implementation of approaches to reduce and control co-existing conditions in cancer free women so if they are diagnosed with breast cancer they are more likely to survive.

## METHODS AND ANALYSIS

### Specific Aims:

#### **In women diagnosed with invasive breast cancer in Missouri between 2002 and 2012 we will:**

1. Examine whether the number or type of co-existing conditions is associated with a higher mortality.
2. Examine whether co-existing conditions have a greater effect on mortality in vulnerable populations including those with low household income, living in rural areas, of African Americans heritage, and the elderly.
3. Examine whether the number of hospitalizations, a surrogate of overall disease severity, post breast cancer diagnoses is higher in women with co-existing conditions and associated with higher mortality.

## **Research Team:**

The investigators include: the Principal Investigator Professor Kala Visvanathan, a breast medical oncologist and cancer epidemiologist that conducts research focused on breast and ovarian cancer prevention; Assistant Professor Avonne Connor, a cancer epidemiologist with a focus on cancer health disparities; Professor Donna Strobino with expertise in women's health and pregnancy outcomes among disadvantaged women; Dr. Jeannette Jackson-Thompson, Director of the Missouri Cancer Registry and Associate Professor, Health Management & Informatics at the University of Missouri School of Medicine and Dr. Chester Lee Schmaltz, Senior Statistician Missouri Cancer Registry and Research Center, University of Missouri.

## **Methods**

### ***Establishment of Cancer Database***

A data set was created that included all women with breast cancer reported to the Missouri Cancer Registry between 2002-2012. Information on first primary breast cancer diagnosis, age at diagnosis, date of diagnosis, tumor characteristics (if lymph nodes are involved, metastatic sites at diagnosis, tumor size, tumor hormone receptor status, tumor stage and grade) cancer treatment date, Census block group (the patient's residence at time of diagnosis, as defined by the 2000 and 2010 Census), neighborhood poverty level, ethnicity (Hispanic vs other), race, county at diagnosis, marital status at diagnosis, rural/urban continuum (based on Beale Code).

Vital statistics information through linkage to the National Death Index was then performed and merged to this data, specifically date and cause of death up till December 31, 2015.

### ***Study Population***

A total of 57,372 women (ages  $\geq 18$  years) diagnosed with breast cancer in Missouri between 2002–2012 were identified from the Missouri Cancer Registry. This data was merged with hospital discharge data from the Missouri Patient Abstract System (n= 53,127 women). Accordingly, 92.6% of women from the Missouri Cancer Registry had hospital discharge data.

A total of 8,569 women from the Missouri Cancer Registry were not incident (first primary) breast cancer cases and were therefore excluded from the present analyses. Women missing survival data in the registry data were also excluded (n=437). The analytical data set was further limited to women who had a hospital visit in the Patient Abstract System the same year as their breast cancer diagnosis ascertained by the registry to ensure that we were evaluating co-existing conditions at the time of diagnosis. The frequency of co-existing conditions among this group was evaluated using the International Classification of Diseases, 9<sup>th</sup> revision (ICD-9) codes.

The top three co-existing conditions identified in the analysis were: essential hypertension, cardiovascular diseases (CVD), type 2 diabetes. Other co-existing conditions included chronic obstructive pulmonary disease, stroke and other cancers. A comorbidity score was also constructed to look for differences in survival between women who had all three co-existing conditions versus 2 or 1.

Researchers then identified women who experienced an inpatient hospitalization more than one year after their breast cancer diagnosis date to ensure hospitalizations were not due to reasons associated with primary breast cancers. A total of 11,303 women experienced a hospitalization based on this criterion. A score was then constructed, based on frequency of total hospitalizations, to evaluate differences in survival. This hospitalization score was categorized as follows: one, two, three, four, and five or more hospitalizations after their breast cancer diagnosis. This score was compared to women without any inpatient hospitalizations after their breast cancer diagnosis. The research team further examined the association between comorbidity score and risk of ever being hospitalized and created an interaction variable between these two variables: never hospitalized; ever hospitalized without one of the three co-existing conditions; and ever hospitalized with one of the three co-existing conditions.

### ***Statistical Analysis***

Descriptive statistics for all primary exposures (type of co-existing condition and comorbidity score) and covariates were generated. Tumor prognostic factors including hormone receptor status and SEER summary stage, initial breast cancer treatment, and demographic factors from the Missouri Cancer Registry data (age at

breast cancer diagnosis, race (White/Caucasian, African American, other races/ethnicities), neighborhood poverty level, and rural/urban residence) were evaluated as covariates. Chi-square tests for categorical variables and t-tests for continuous variables were used to compare descriptive results by race/ethnicity. The outcomes of interest included breast-cancer specific mortality and all-cause mortality.

Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by stratified Cox proportional hazards regression models for associations with mortality outcomes overall and by our selected groups. Final models for evaluation of the associations between co-existing conditions and mortality outcomes were adjusted for other co-existing conditions (with diabetes, hypertension, and CVD as main effects), age at diagnosis, race, breast cancer stage, estrogen/progesterone receptor (ER/PR) status, breast cancer treatment, and urban/rural residence. Final models for the associations between hospitalization score and mortality outcomes were adjusted for comorbidity score, age at diagnosis, race (all women), SEER stage, ER/PR status, breast cancer treatment, and urban/rural location and models for the association between the interaction of hospitalization and comorbidity status were also adjusted for these covariates. The proportional hazards assumption was tested statistically using an interaction of main effects and covariates with the log of survival time. Adjusted odds ratios (ORs) and 95% CIs were also calculated using multivariable logistic regression models for associations between comorbidity score and risk of hospitalizations. Interactions between primary comorbidity exposures and our selected groups (race/ethnicity, neighborhood poverty level, urban vs. rural residency, and age) were assessed using the likelihood-ratio test comparing the model including an interaction term with a reduced model without the term. A p value < 0.05 was considered potentially important for main effects and for interactions. All data analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

### **Results:**

Of the total, 36,581 women with invasive breast cancer and with hospital discharge data within the same year of their breast cancer diagnosis were included in the results. Most of the women were white (88.7%), approximately 10% were African American, and only 1.4% identified as another race. The average age at breast cancer diagnosis was significantly different by race (whites, 62.2 years; African Americans, 58.5 years; other races, 56 years). After a median follow-up time of 6.5 years (78 months), 11,102 deaths occurred, of which 56% (N = 6,232) of deaths were due to breast cancer.

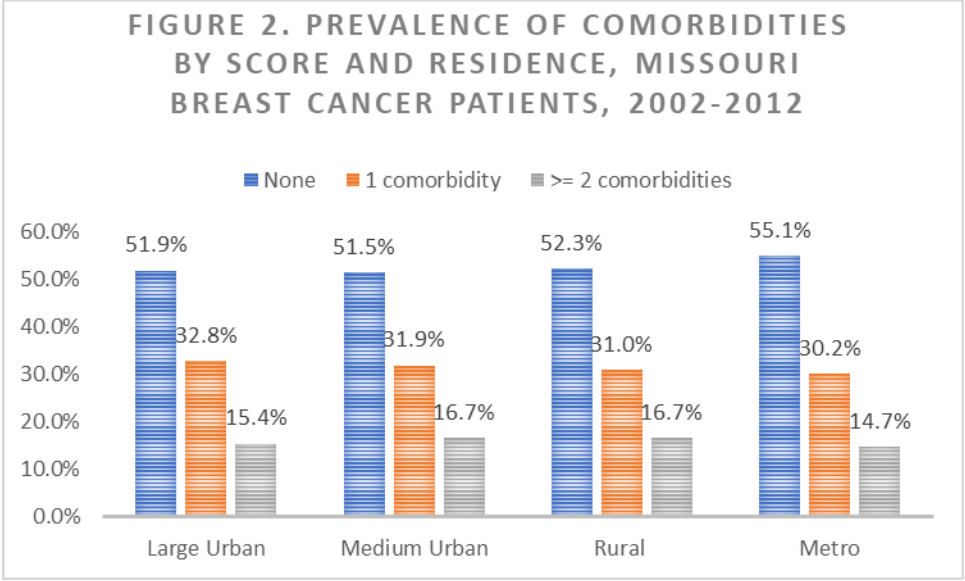
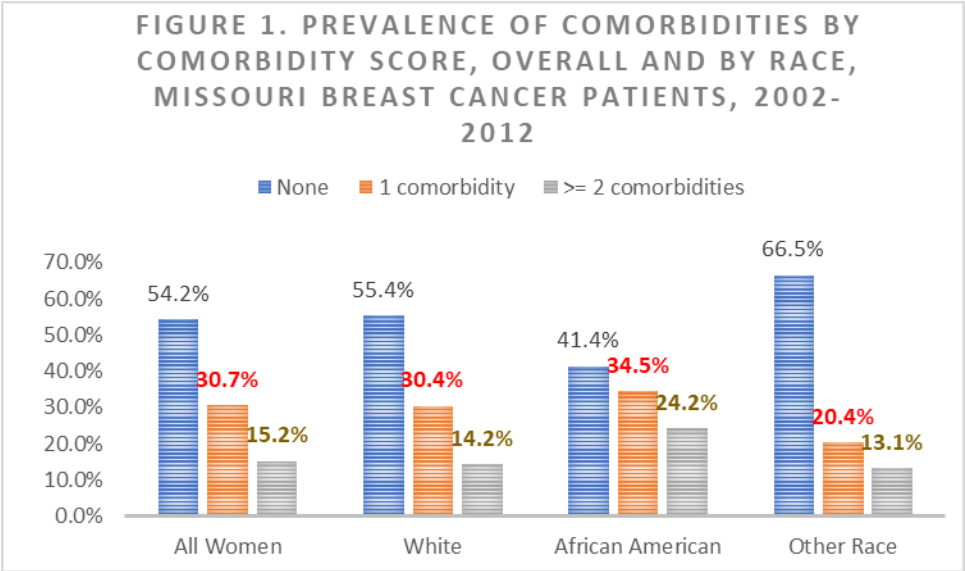
**Median survival times were significantly different by race groups, with African American breast cancer patients having the lowest median survival (69 months) compared to white women (79 months) (p value < 0.001).**

A higher proportion of African American women were diagnosed with distant stage (9.4%) compared to non-Hispanic whites and other races (both 5%). This difference may be partly explained by the fact that almost 26% of African American breast cancer patients were diagnosed with a more aggressive subtype ER-/PR- tumors compared to 14.4% of white women (chi-square p value < 0.001).

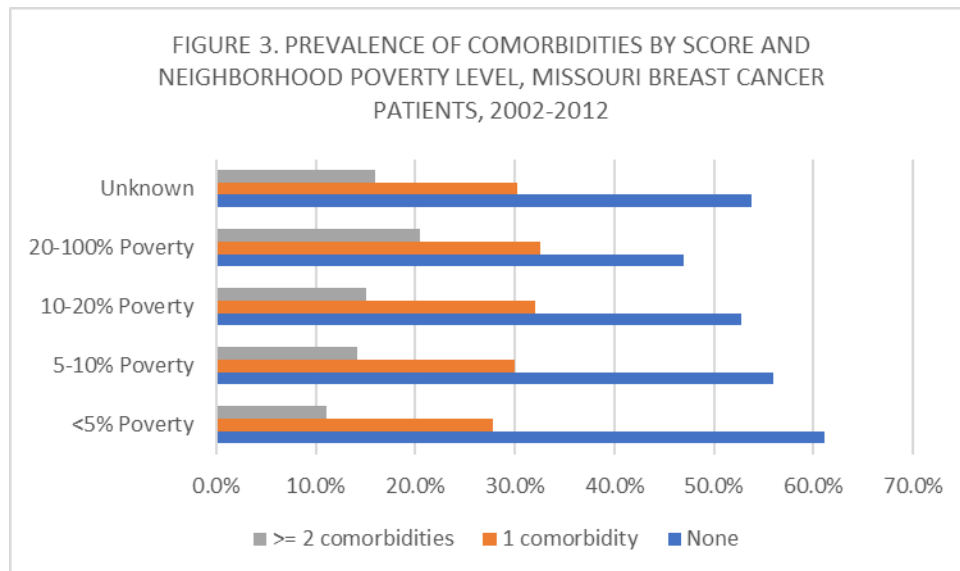
**For breast cancer -specific and all-cause survival as expected age, stage and tumor subtype were very important predictors for length of survival, and marital status and rural/urban residence moderately so.**

### **Co-existing Conditions and Comorbidity Score:**

The three most prevalent non-cancer co-existing conditions identified at the time of breast cancer diagnosis were type 2 diabetes, essential hypertension, and CVD. As shown in Figure 1, a total of 46% of women had at least one of the three co-existing conditions. A total of 30.7% of women had at least one co-existing condition, and 15.2% had two or more co-existing conditions. The prevalence of comorbidity was higher among African American women with over half having at least one co-existing condition (34.5% had at least one co-existing condition while 24.2% had two or more). (See Figure 1).



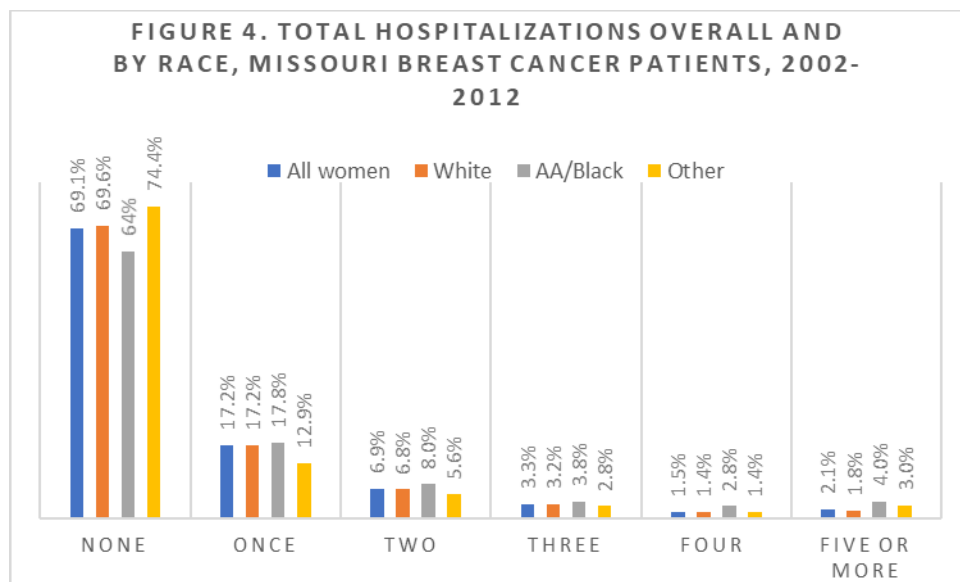
As shown in Figure 2 breast cancer patients in large urban areas versus rural areas have a greater prevalence of co-existing conditions. (chi-square p value < 0.001).



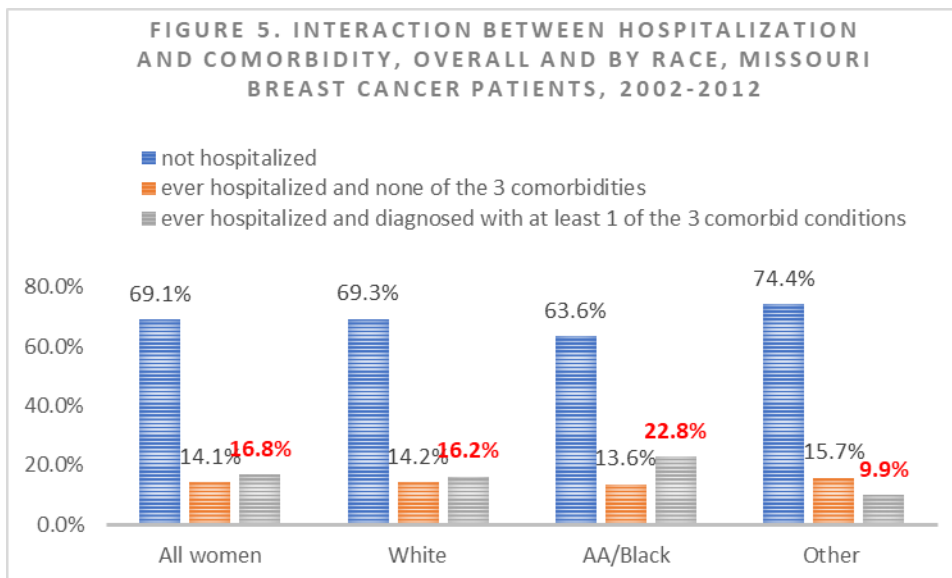
The prevalence of co-existing conditions by comorbidity score also differed by neighborhood poverty level (chi-square p value < 0.01). Figure 3 demonstrates these differences: A higher percentage of women living in neighborhoods with >20% of the poverty level were burdened by 2 or more co-existing conditions (20.5%) compared to breast cancer patients living in neighborhoods with <5% of the national poverty level (11.1%). **The results suggest that the higher the poverty level the greater the prevalence of co-existing conditions.**

**Hospitalizations:**

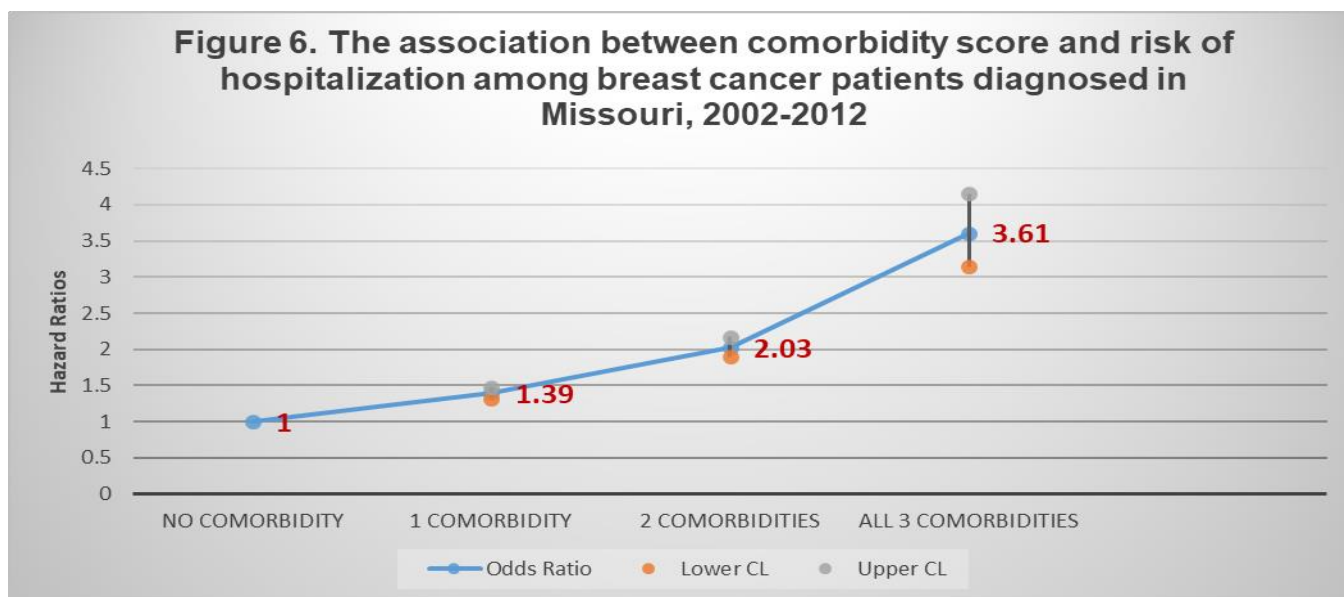
African American women had more hospitalizations compared to whites and other races one-year post breast cancer diagnosis. (Figure 4).



Approximately 23% of African American women who experienced a hospitalization had at least one of three co-existing conditions (diabetes, HBP, or CVD) (Figure 5).



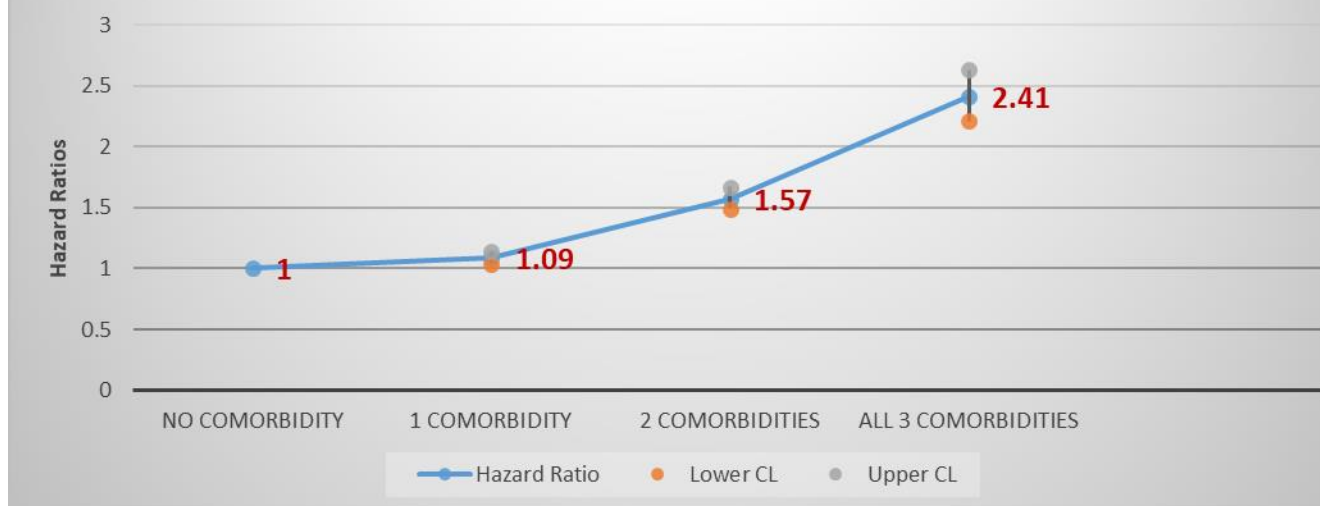
Women with all three co-existing conditions were over three times more likely to ever be hospitalized compared to women without diabetes, HBP, and CVD (Figure 6).



### ***Associations between Co-existing Conditions and All-Cause Mortality***

Breast cancer patients with CVD had the highest risk of all-cause mortality (HR, 1.70; 95% CI 1.62-1.79), followed by diabetes (HR, 1.37; 95% CI 1.30-1.45). An increasing number of co-existing conditions was significantly associated with all-cause mortality ( $p_{\text{trend}} < 0.001$ ) (Figure 7). Women with just one co-existing condition had an increased risk of death of 9% compared to women without diabetes, hypertension, and CVD (HR, 1.09; 95% CI 1.04-1.14). **Breast cancer patients with all three co-existing conditions had over a 200% increase in risk of death compared to those without these three co-existing conditions (HR, 2.41; 95% CI 2.21-2.63).**

**Figure 7. The association between comorbidity score and risk of all-cause mortality among breast cancer patients diagnosed in Missouri, 2002-2012**

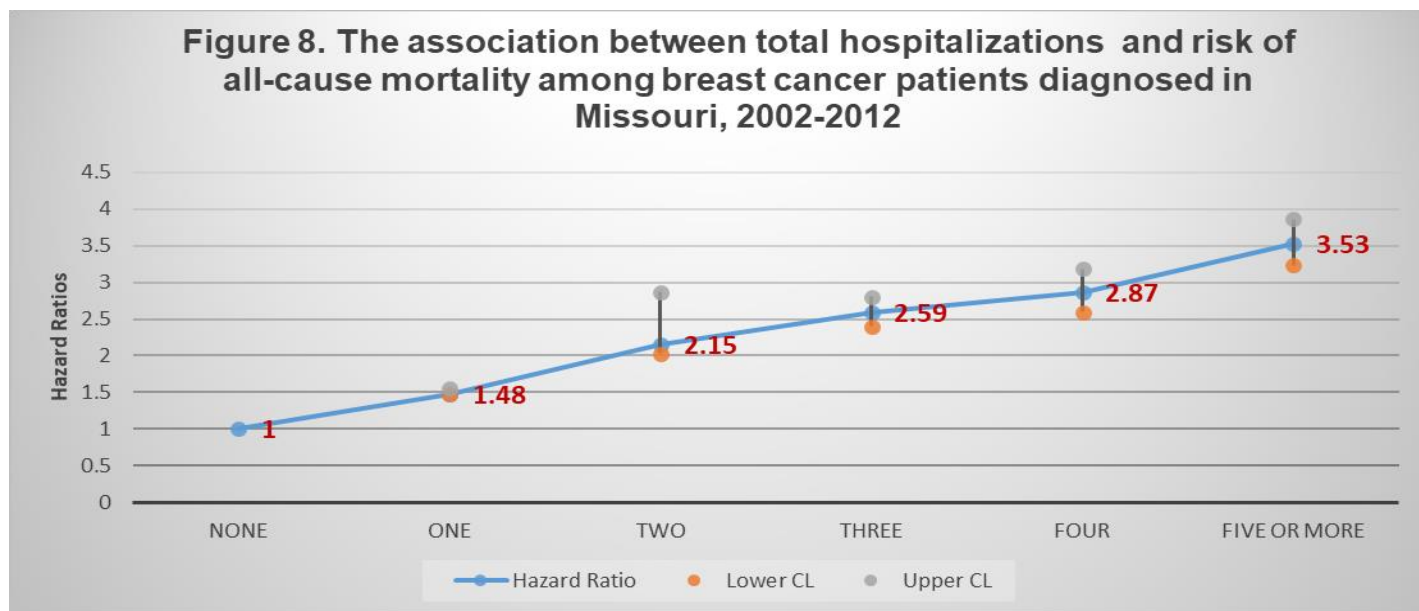


In stratified analyses, there were significant differences in associations with comorbidity score by race ( $p=0.001$ ), and poverty ( $p=0.04$ ). There was also a statistically significant interaction with age when modeled as a continuous measure, comorbidity score, and risk of all-cause mortality ( $p < 0.001$ ). **In results stratified by rural/urban residence, women living in large urban areas with all three co-existing conditions were more than three times more likely to die of any cause (HR, 3.34; 95% CI 2.36-4.74).**

***Associations between Hospitalizations and All-cause Mortality Results***

Increasing number of hospitalizations was significantly associated with all-cause mortality ( $p_{\text{trend}} < 0.001$ ). **Breast cancer patients with five or more hospitalizations had over a 300% increase in risk of death compared to those without hospitalizations (HR, 3.53; 95% CI 3.23-3.86) (See Figure 8).**

**Figure 8. The association between total hospitalizations and risk of all-cause mortality among breast cancer patients diagnosed in Missouri, 2002-2012**





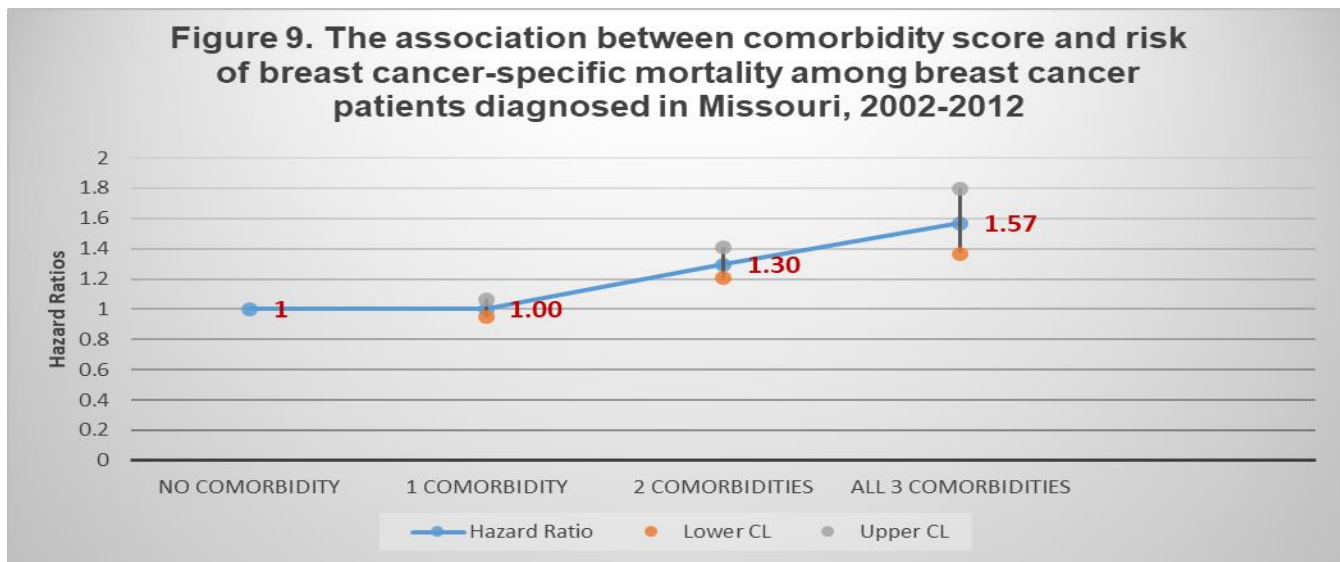
Significant differences in associations with hospitalizations and all-cause mortality were observed by race (AA compared to whites:  $p=0.01$ ), rural/urban location ( $p=0.002$ ), and age ( $p < 0.001$ ). **Interestingly, women under the age of 50 years with five or more hospitalizations had the highest risk of dying (HR, 7.36; 95% CI 5.88-9.22).** African American women with five or more hospitalizations had almost a 4-fold risk of all-cause mortality (HR, 3.89; 95% CI 3.15-4.80).

### Association between Co-existing Conditions, Hospitalization and All-Cause Mortality

Breast cancer patients with a co-existing condition who are hospitalized have a higher mortality than those who are not. The cause of the hospitalization could be related to their co-existing condition, or to cancer or other conditions. This is yet to be explored. The risk of death increases with the number of hospitalizations. For those women with five or more hospitalization their risk is more than 200% greater than women that are not hospitalized (HR = 2.82, 95%CI 2.50-3.20)

### Breast Cancer Mortality Results for Co-existing Conditions and Comorbidity Score

Researchers also evaluated breast cancer mortality. Among all women, breast cancer patients with CVD had 35% higher risk of breast cancer mortality (HR, 1.35; 95% CI 1.26-1.46), compared to patients with no co-existing conditions. The association was even stronger among African American women (HR, 1.72; 95% CI 1.42-2.08). Breast cancer patients with diabetes had a 22% higher increase in mortality compared to patients without diabetes (HR, 1.22; 95% CI 1.13-1.31). **Further the greater the number of co-existing conditions the higher the risk of breast cancer mortality ( $p_{\text{trend}} < 0.001$ ) (Figure 9). Specifically, women with 2 co-existing conditions had a 30% increase in breast cancer mortality and with three co-existing conditions a 57% increase in breast cancer mortality.**

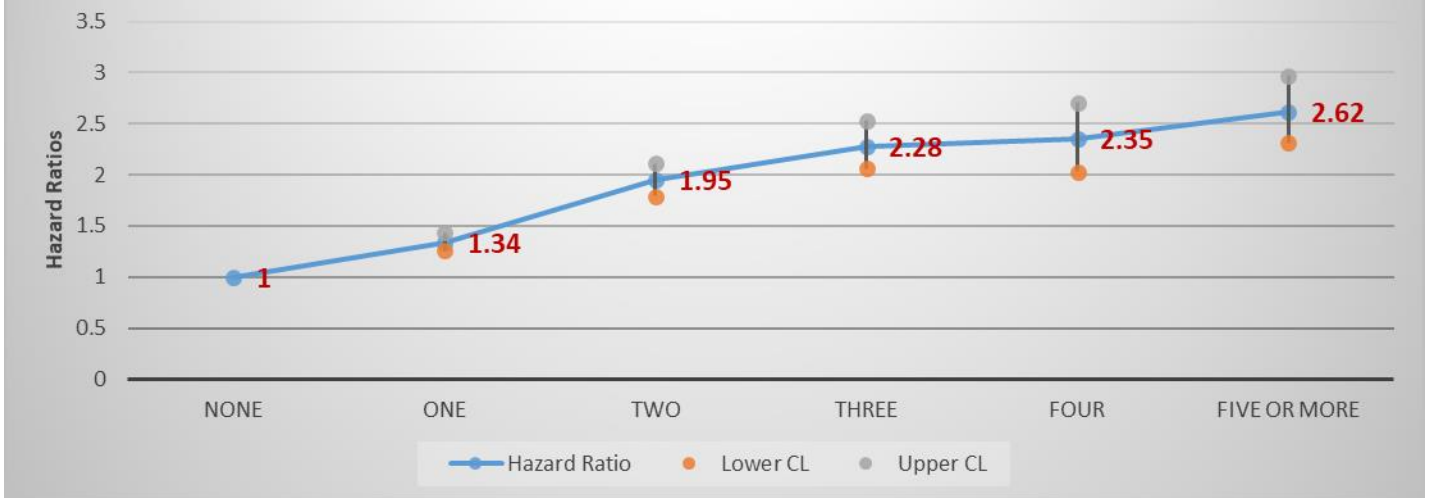


In stratified analyses, researchers did not observe significant differences in breast cancer-specific mortality for specific subgroups (race, neighborhood poverty level, rural/urban residence, breast cancer subtypes) but associations were increased in all groups. There was a statistically significant interaction with age when modeled as a continuous measure ( $p < 0.001$ ). With increasing age, the risk of breast cancer mortality also increased among women with co-existing conditions.

### Breast Cancer Mortality Results for Hospitalizations

Breast cancer patients with five or more hospitalizations also had increased risk of breast-cancer mortality (HR, 2.62; 95% CI 2.31-2.97) Figure 10. **Having just one hospitalization increased the risk of dying from breast cancer by 34% among all women (HR, 1.34; 95% CI 1.26-1.43) compared to women without a hospitalization.**

**Figure 10. The association between total hospitalizations and risk of breast cancer-specific mortality among breast cancer patients diagnosed in Missouri, 2002-2012**



In stratified analyses, researchers observed significant differences in associations between hospitalizations and breast cancer mortality by race ( $p=0.02$ ), urban/rural location ( $p < 0.01$ ), and age ( $p < 0.001$ ). African American women with five or more hospitalizations (HR, 3.14; 95% CI 2.40-4.10) had higher risk of breast cancer death compared to white women (HR, 2.47; 95% CI 2.14-2.86) with five or more. **Women less than 50 years of age and with five or more hospitalizations had over 600% increase in risk of breast cancer death compared to women under 50 years old without hospitalizations (HR, 6.51; 95% CI 5.12-8.29).**

### Strengths of the Study

- Representative of the entire state over many years
- Large sample
- Takes advantage of high quality data generated in Missouri

### Future Possibilities

With additional funding, researchers have the potential to look more carefully at the reasons behind the hospitalizations, and can consider merging this data to Medicaid and Medicare which would clarify these findings further.

### References

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