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Identifying Typologies of Breast Cancer Patients Based on Multiple Individual and Contextual Factors for Timely Treatment Initiation

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

Sharon Hyun Baik

Committee in charge:

University of California San Diego

Professor Carrie R. McDonald
Professor Georgia Robins Sadler

San Diego State University

Professor Vanessa L. Malcarne, Co-Chair
Professor Kristen J. Wells, Co-Chair
Professor Scott C. Roesch

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The Dissertation of Sharon Hyun Baik is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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_____
Co-chair

_____
Chair

University of California San Diego
San Diego State University
2018

DEDICATION

This dissertation is dedicated to my mother, whose undeniable strength, courage, and resilience have inspired me and sparked my journey in psycho-oncology, and to my father and brother who have taught me the values of patience and the unbreakable bond of family. To all of my family, Baiks and Songs, and friends who are like family— I am forever grateful and blessed for all your love and support, especially throughout graduate school, and for reminding me of my purpose and that there is light at the end of the tunnel.

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VITA

2010	Bachelor of Arts, University of California, Berkeley
2015	Master of Science, San Diego State University
2018	Doctor of Philosophy, University of California San Diego and San Diego State University

PUBLICATIONS

Pan, T. M., Mills, S. D., Fox, R. S., **Baik, S. H.**, Harry, K. M., Roesch, S. C., Sadler, G. R., & Malcarne, V. L. (2017). The psychometric properties of English and Spanish versions of the Life Orientation Test-Revised in Hispanic Americans. *Journal of Psychopathology and Behavioral Assessment. 39, 657-668.*

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ABSTRACT OF THE DISSERTATION

Identifying Typologies of Breast Cancer Patients Based on Multiple Individual and Contextual Factors for Timely Treatment Initiation

by

Sharon Hyun Baik

Doctor of Philosophy in Clinical Psychology

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Professor Vanessa L. Malcarne, Co-Chair
Professor Kristen J. Wells, Co-Chair

Rationale: Breast cancer is the most commonly diagnosed cancer, excluding skin cancers, and is the second leading cause of cancer death among women in the United States. Despite advancements in screening, early detection, and cancer treatments, not all women have benefited equally. Racial and ethnic minorities, particularly African American women, and those of low income have higher breast cancer mortality rates compared to the general population. Previous research has identified a number of demographic (e.g., race/ethnicity, age, health insurance, income), medical (e.g., comorbidities with other illnesses, family medical history), environmental (e.g., geographic area), and health system (e.g., type of cancer-related services available) factors associated with breast cancer disparities. However,

these factors have largely been examined individually, and no study has comprehensively evaluated how multiple individual and contextual factors impact breast cancer outcomes. Therefore, this dissertation project had two primary aims: 1) to identify distinct subgroups of breast cancer patients based on demographic, medical, environmental, and health system factors that have been shown to influence timeliness of breast cancer care, and 2) to examine differences among emergent classes in timely initiation of breast cancer treatment.

Design: The proposed study used archival data from the control arm of the Patient Navigation Research Project (PNRP), a five-year 10-site clinical trial of adult patients from medically underserved populations with an abnormal cancer screening or a new diagnosis of breast, cervical, colorectal, or prostate cancer. For this study, the sample included 198 patients with newly diagnosed Stage I-III breast cancer who received usual standard of care (control arm) from four PNRP sites, and who received a treatment for breast cancer (e.g., surgery, chemotherapy, radiation, hormonal therapy). Control participants were primarily recruited via medical record abstraction for which informed consent was waived. Exploratory Latent Class Analysis (LCA) was used to identify subgroups of breast cancer patients based on demographic (race/ethnicity, age at diagnosis, health insurance status, annual household income), medical (comorbidities [Charlson Comorbidity Index], family history of cancer), environmental (geographic residence [urban vs. rural], and health system (cancer-related services available onsite) factors associated with timeliness of breast cancer care. For the second aim, the study conducted logistic regression analyses to examine if class membership significantly predicted timely breast cancer treatment initiation, defined as initiation of any treatment for breast cancer (e.g., surgery, chemotherapy, radiation, hormonal therapy) within 30 or 60 days of diagnosis, controlling for type of breast cancer treatment.

Results: Three classes of breast cancer patients were identified with varying patterns of patient demographic, medical, and health system characteristics. The first class was distinguished by its high endorsement of indicators associated with timely breast cancer care; patients in this class were most likely to be White, have private health insurance, and have a family history of cancer. The second class was characterized by individual and contextual factors associated with treatment delays, including having public health insurance, not having a family history of cancer, and receiving care at a facility with the least amount of breast cancer services available onsite. The third class represented breast cancer patients with the oldest average age at diagnosis and the greatest number of medical comorbidities. Binomial logistic regression analyses demonstrated that the emergent classes did not significantly differ in the likelihood of initiating breast cancer treatment within 30 days or 60 days from breast cancer diagnosis, controlling for type of treatment.

Conclusions: The present study used LCA to derive classes of breast cancer patients based on simultaneous evaluation of demographic, medical, environmental, and health system factors associated with timely breast cancer care. However, the emergent classes did not significantly differ in terms of timely initiation of breast cancer treatment following definitive diagnosis of breast cancer. The relatively small and homogenous study sample may have obscured differences in timeliness of breast cancer treatment initiation. Future studies should utilize LCA with larger, more diverse samples of breast cancer patients to identify distinct classes with unique combinations of individual and contextual characteristics that influence timeliness of breast cancer care. Identification of distinct typologies of breast cancer patients provides a deeper understanding of how the combination of factors synergistically impacts

breast cancer outcomes and can help target interventions to specific subgroups of patients that are most likely to experience delays in breast cancer care.

CHAPTER 1: INTRODUCTION

1.1 Breast Cancer in the United States

Breast cancer is the most commonly diagnosed cancer, excluding skin cancers, and is the second leading cause of cancer death among women in the United States (American Cancer Society, 2018). In 2018, an estimated 266,120 new cases of invasive breast cancer will be diagnosed in women, and approximately 40,920 will die of this disease (American Cancer Society, 2018). About 1 in 8 (12.4%) women in the United States will develop breast cancer during their lifetime (American Cancer Society, 2017). Most breast cancers and breast cancer deaths occur in women aged 55 years and older. The median age at diagnosis of breast cancer is 62 years (American Cancer Society, 2017) Overall, 62% of breast cancers are diagnosed at a localized stage (cancer confined to the breast), 31% at a regional stage (cancer spread to regional lymph nodes), and 6% at a distant stage (cancer metastasized to distant organs or lymph nodes) (Howlader et al., 2017). The overall 5-year relative survival rate for breast cancer is 91%, and is higher when breast cancer is detected and treated early: the 5-year relative survival rate for localized breast cancers is 99% compared to 85% for regional stage and 27% for distant stage breast cancers (American Cancer Society, 2017).

Incidence rates for breast cancer in the United States have remained stable from 2004 to 2014, after decreasing 2.3% per year from 1999 to 2004 (Siegel, Miller, & Jemal, 2018). However, breast cancer incidence and mortality rates vary substantially by race/ethnicity. Non-Hispanic white (White) and non-Hispanic African American (African American) women have higher incidence and mortality rates than Hispanic and American Indian/Alaska Native (AI/AN) women (Copeland et al., 2015). Asian/Pacific Islander (A/PI) women have the lowest breast cancer incidence (90.7 per 100,000) and mortality (11.3 per 100,000) rates

(American Cancer Society, 2017). A/PI and White women have the highest proportions of localized breast cancers (65%-67%) and lowest proportions of regional (27%-30%) stage cancers (DeSantis, Ma, Goding, Newman, & Jemal, 2017). Five-year cause-specific breast cancer survival is highest for A/PI women for every stage of disease. Lower breast cancer rates in A/PI, Hispanic, and AI/AN women may reflect variation in the prevalence of risk factors for breast cancer (American Cancer Society, 2017; Chlebowski et al., 2005). For example, A/PI women have lower rates of alcohol consumption and obesity, and are more likely to breastfeed for at least 12 months, both of which are factors commonly associated with lower breast cancer risk (Blackwell, Lucas, & Clarke, 2014; Centers for Disease Control and Prevention, 2015; Fedewa, Sauer, Siegel, & Jemal, 2015). Conversely, compared to other races/ethnicities, Hispanic women tend to have a greater number of children and AI/AN women tend to have their first child at younger ages, both of which are considered protective factors against breast cancer (Martin, Hamilton, Osterman, Curtin, & Matthews, 2015).

From 1989 to 2015, overall breast cancer mortality rates have declined by 39%, after slowly increasing for many years (0.4% per year) since 1975 (American Cancer Society, 2017). As a result of this decline, 322,600 breast cancer deaths have been averted in United States women from 1990 to 2015. Declines in breast cancer mortality have been attributed to advancements in cancer treatments (e.g., adjuvant chemotherapy and hormonal therapy in the 1980s; targeted therapies in the 1990s) and early detection (Berry et al., 2005; Brawley & Berger, 2008; Munoz et al., 2014). However, not all women in the United States have benefited equally from these advances.

Although the overall breast cancer incidence rate in African American women is lower than in White women (125.5 vs. 128.7 cases per 100,000), African American women have a

higher breast cancer mortality rate (29.5 vs. 20.8 cases per 100,000) and a lower 5-year breast cancer survival rate (83% vs. 92%) compared to White women (American Cancer Society, 2017). This significant divergence in breast cancer mortality trends between African American and White women first emerged in the early 1980s (American Cancer Society, 2017). While overall breast cancer mortality rates have declined in both African American and White women, the decline has been slower in African American women resulting in a widening disparity. Since 1990, breast cancer mortality rates dropped 23% in African American women compared to 37% in White women (American Cancer Society, 2016b), and by 2015, breast cancer mortality rates were 39% higher in African American women than in White women (American Cancer Society, 2017). Additionally, overall breast cancer incidence rates increased in African American women by 0.4% from 2005 to 2014 compared to stable rates in White women (American Cancer Society, 2017), and African American women have a higher incidence of breast cancer before age 40 and a younger median age at diagnosis than in White women (59 vs. 63 years; Howlader et al., 2017). They are also more likely to be diagnosed with more advanced breast cancers, as well as more aggressive, triple negative breast cancer. Compared to women of other race/ethnicities, African American women have the highest proportions of regional (34%) and distant (9%) stage breast cancers, and have the lowest 5-year breast cancer survival across all known diagnostic stages (DeSantis et al., 2017).

Hispanic women have lower rates of breast cancer incidence (91.9 per 100,000) and mortality (14.2 per 100,000) compared to African American and White women (American Cancer Society, 2015b, 2017), but breast cancer is the most common cancer and leading cause of cancer death for this population (American Cancer Society, 2015b). Hispanic women also tend to be diagnosed with later-stage breast cancers (American Cancer Society, 2015b), which

may be due to their lower screening mammography rates and delays in follow-up after an abnormal mammogram (American Cancer Society, 2015b). They also experience a greater number of barriers to screening (e.g., health insurance, system problems with scheduling care) compared to other ethnic minorities and White women (Ramachandran et al., 2015).

1.2 Breast Cancer Treatment

The treatment of breast cancer is complex and varied, and includes local therapy, such as surgery and radiation therapy, and systemic therapy, such as chemotherapy, hormone therapy, and targeted therapy (American Cancer Society, 2017). Systemic treatment given to patients before surgery or after surgery is called neoadjuvant therapy or adjuvant therapy, respectively. Breast cancer treatment plans differ for patients based on the disease stage and tumor characteristics, comorbidities, patient's age and preferences, and the associated risks and benefits of each option (American Cancer Society, 2017).

Surgery. Surgical treatment for breast cancer involves breast-conserving surgery (BCS; also known as lumpectomy or partial mastectomy) or mastectomy. In BCS, only the part of the breast containing the cancer is removed, while in mastectomy, the entire breast is removed, including all of the breast tissue and sometimes other nearby tissue (American Cancer Society, 2017). The primary goals of surgery are to remove the cancer from the breast and to determine the stage of cancer (American Cancer Society, 2017). Removal of one or more regional lymph nodes from the armpit is usually conducted with breast cancer surgery to determine if the cancer has spread beyond the breast, which helps stage the disease (American Cancer Society, 2017). If cancer cells are found in the lymph nodes, subsequent surgery, radiation therapy, and/or systemic therapy may be needed. Surgery is the primary treatment

for early stage breast cancers, and is often combined with other treatments to reduce the risk of recurrence.

Radiation Therapy. Radiation is often used after surgery to destroy the remaining cancer cells in the breast(s), underarm area, or chest wall (American Cancer Society, 2017). Radiation therapy is almost always followed after BCS, as it has been shown to reduce the risk of breast cancer recurrence and breast cancer death by 50% and 20%, respectively, in most patients (Darby et al., 2011), and also benefits mastectomy-treated patients if their cancer is found in the lymph nodes or their tumor is larger than 5 cm (American Cancer Society, 2017).

Chemotherapy. Chemotherapy drugs generally work by attacking cancer cells, and the benefit of chemotherapy depends on multiple factors, including tumor size, number of lymph nodes, presence of estrogen [ER] or progesterone [PR] receptors, and excess levels of human epidermal growth factor receptor 2 (HER2) protein (American Cancer Society, 2017). "Triple negative" (ER-negative [ER-], PR-negative [PR-], HER2-negative [HER2-]) and HER2-positive (HER2+) breast cancers are generally more sensitive to chemotherapy, whereas ER-positive (ER+) and/or PR-positive (PR+) breast cancers tend to be less responsive (von Minckwitz et al., 2012). There are several chemotherapy drugs available for breast cancer and a typical chemotherapy regimen includes a combination of drugs, which has been to be more effective than a single chemotherapy drug for treatment of early stage breast cancer (American Cancer Society, 2017). Neoadjuvant and adjuvant chemotherapy is usually administered for three to six months, and treatment is most effective when the full cycle and dose of drugs are completed in a timely manner, without interruptions or premature

completions, and without significant delays in initiating treatment (American Cancer Society, 2017; von Minckwitz et al., 2012).

Hormone-blocking Therapy. Hormone-blocking (endocrine) therapy is given to patients with hormone receptor-positive (ER+/PR+) breast cancers to lower or block the effects of estrogen that promotes the growth of breast cancer cells (American Cancer Society, 2017). Tamoxifen is generally used to treat premenopausal and postmenopausal breast cancers, as tamoxifen has been shown to reduce the rate of breast cancer recurrence and mortality by about 40% – 50% throughout the first 10 years and about 33% throughout the first 15 years, respectively, in women with ER+ breast cancers (Early Breast Cancer Trialists' Collaborative Group, 2011). Aromatase inhibitors (AIs; e.g., letrozole, anastrozole, and exemestane) are also used to treat ER+/PR+ breast cancers, and treatment guidelines currently recommend including AIs to the treatment of postmenopausal women with ER+/PR+ breast cancers (Burstein et al., 2010).

Targeted Chemotherapy. About 14% of breast cancers overproduce HER2 growth-promoting protein and there are several medications approved to treat this subtype (American Cancer Society, 2017). Therapy aimed at HER2 includes trastuzumab (Herceptin) and pertuzumab (Perjeta), which is generally used in combination with standard chemotherapy to treat HER2+ breast cancers. Large clinical trials have demonstrated that adding trastuzumab to chemotherapy for early stage HER+ breast cancer reduces the risk of breast cancer recurrence and mortality by 52% and 33%, respectively (Wolff et al., 2013), and combining pertuzumab with docetaxel (Taxotere) and trastuzumab prolongs survival by over 15 months compared to either docetaxel or trastuzumab alone (Swain et al., 2015).

Breast Cancer Treatment Guidelines. The National Comprehensive Cancer Network (NCCN; 2016) provides evidence-based clinical practice guidelines for standard treatment of invasive (stage I–III) breast cancer based on several prognostic and predictive factors, including tumor histology and characteristics, axillary lymph node status, hormone receptor status, HER2 status, comorbid conditions, menopausal status, and patient age. Specific treatment recommendations are based on results of past and present clinical trials demonstrating evidence of its efficacy, and uniform NCCN consensus that the intervention is appropriate.

1.3 Breast Cancer Disparities

Disparities in breast cancer outcomes likely reflect a combination of biologic and nonbiologic factors, including advanced stage at diagnosis, more aggressive tumors, other comorbidities, and unequal access to timely, high-quality breast cancer care (American Cancer Society, 2017; Barry & Breen, 2005; Komenaka et al., 2010; Trufelli, Matos, Santi, & Del Giglio, 2015). Although underuse of screening mammography and lack of diagnostic follow-up after an abnormal mammogram result have been linked to racial/ethnic disparities in breast cancer mortality (Bickell, 2002; Bowen, Stebbing, & Jones, 2006), use of screening mammography is now nearly equivalent among African American (69%), A/PI (69%), and White (70%) women, with slightly lower mammography rates in Hispanic (64%) and AI/AN (61%) women (American Cancer Society, 2015a; Bickell, 2002; Breen, Wagener, Brown, Davis, & Ballard-Barbash, 2001). There is growing evidence that factors independent of breast cancer stage and tumor characteristics, such as treatment differences, may explain a significant portion of disparate breast cancer outcomes (Dignam, Redmond, Fisher,

Costantino, & Edwards, 1997; O'Brien et al., 2010; Shavers & Brown, 2002; Tammemagi, 2007; Yood et al., 1999).

Racial/ethnic minorities, particularly African American and Hispanic women, have been shown to be less likely to receive the standard recommended treatments for breast cancer (Bickell et al., 2006; Chen & Li, 2015; Freedman, He, Winer, & Keating, 2009; Haggstrom, Quale, & Smith‐Bindman, 2005; Hershman et al., 2005; Ooi, Martinez, & Li, 2011; Shavers & Brown, 2002). In a recent analysis of 18 population-based cancer registries, across several states in the United States, African American and Hispanic women with stage I or II breast cancer had a significant 40% and 30%, respectively, higher risk of not receiving guideline-concordant treatment for breast cancer overall and across subtypes, except HR-/HER2+ (Chen & Li, 2015). Specifically, African American women had a 30% to 60% higher risk of receiving non-guideline-concordant-treatment for HR+/HER2- (OR = 1.3; 95% CI: 1.2 – 1.5), HR+/HER2+ (OR = 1.4; 95% CI: 1.0 – 1.8), and triple negative (HR-/HER2-; OR = 1.6; 95% CI: 1.3 – 2.0) breast cancers; while Hispanic women had a 30% to 40% higher risk of receiving non-guideline-concordant treatment for HR+/HER2- (OR = 1.3; 95% CI: 1.1 – 1.4) and HR+/HER2+ (OR = 1.4; 95% CI: 1.1 – 1.9). Studies have demonstrated that when women across racial/ethnic groups receive equal treatments, they have similar breast cancer outcomes (Dignam, 2000, 2001; Dignam et al., 1997; Du, X. L., Fang, & Meyer, 2008; Heimann et al., 1997; McCaskill-Stevens et al., 2004; Perkins, Cooksley, & Cox, 1996; Yood et al., 1999). Recently, research has begun focusing on the timeliness of breast cancer treatment, and delay in initiation of treatment has been proposed as a potential mechanism contributing to disparate breast cancer survival outcomes.

1.4 Timeliness of Breast Cancer Treatment

There are currently no professional or practice guidelines for oncologists indicating standard of care for the timeliness of breast cancer treatment. Consequently, research evaluating treatment delays has used multiple starting points, including from breast cancer related abnormalities, biopsy, diagnosis, and surgery, to describe the time to treatment interval, and has used multiple time intervals to define treatment delays. A recent review of breast cancer treatment delays on prognosis and survival, which included 33 studies from 14 countries, found substantial variation in the definition of treatment delay and interval length (Williams, F., 2015). For example, studies defined the interval to treatment as the time from the date of biopsy and/or diagnosis to the start of treatment in general or in specific treatments, such as surgery, chemotherapy, radiation, or endocrine therapy; or time from surgery to the start of first radiation or first chemotherapy treatment. Additionally, studies varied in the time interval that constituted treatment delay, and categorized delay intervals in days, which ranged from 0 to > 180 days, in weeks, which ranged from 0 to > 26 weeks, or in months, which ranged from 0 to > 3 months.

Treatment Delay and Survival. Longer wait times from point of diagnosis to initiating breast cancer treatment has prognostic concern as delays can result in disease progression, potential worsening of disease, or even death. In a retrospective analysis of 1,786 low-income,-adult female North Carolina Medicaid enrollees diagnosed with breast cancer, McLaughlin et al. (2012) evaluated the impact of longer intervals between biopsy-confirmed breast cancer diagnosis to initiation of treatment (e.g., surgery, radiotherapy, chemotherapy, or hormonal/biologic therapy) on survival. Among late-stage (regional or distant) breast cancers, treatment delays ≥ 60 days from diagnosis were associated with significantly (66% for regional and 85% for distant) increased risk of overall mortality (HR = 1.66; 95% CI:

1.00–2.77; $p = .05$) and breast cancer-related mortality (HR = 1.85; 95% CI: 1.04–3.27; $p = .04$). While a 3-month or longer delay between diagnosis and treatment initiation (e.g., surgery, chemotherapy, radiation, or hormonal therapy) has also been shown to decrease survival (Gorin, Heck, Cheng, & Smith, 2006; Lund et al., 2008), several other studies have found that delays in adjuvant treatment > 3 months from diagnosis do not influence survival (Brazda et al., 2010; Eastman et al., 2013; Elmore et al., 2005; Hershman et al., 2005; Smith, E. R. et al., 2008).

Diagnosis to surgery. Two independent population-based studies using national data from the Surveillance, Epidemiology, and End Results (SEER)–Medicare–linked database and the National Cancer Database (NCDB) evaluated five time-to-surgery intervals (≤ 30, 31–60, 61–90, 91–120, and 121–180 days) and found that longer time from diagnosis to surgery was associated with a decline in overall survival among patients diagnosed with stage I–III breast cancer (Bleicher et al., 2016). The increase in overall mortality for each interval increase in treatment delay was 9% in the SEER–Medicare cohort (HR = 1.09; 95% CI: 1.06–1.13; $p < .001$) and 10% in the NCDB cohort (HR = 1.10; 95% CI: 1.07–1.13; $p < .001$), and greater time to surgery was significantly associated with lower overall survival in stage I and II breast cancers, but not stage III. In a retrospective case-only study of 8,860 adolescent and young adult (AYA; women aged 15 to 39 years) breast cancer patients, young women who were treated by surgery and had treatment delay > 6 weeks from diagnosis had worse 5-year survival than those who had their surgery within 2 weeks of diagnosis (80% vs. 90%, respectively; $p = .005$; Smith, E. C., Ziogas, & Anton-Culver, 2013). Longer treatment delay (> 6 weeks) from diagnosis to surgery was also a significant, independent risk factor for

shorter survival at 60 months (HR = 1.82; 95% CI: 1.21–2.74; p = .03) compared to shorter treatment delay (< 2 weeks).

Surgery to adjuvant treatment. Trufelli et al. (2015) conducted a retrospective cohort review of 348 women diagnosed with breast cancer and found women with a delay > 4 months from surgery to first adjuvant treatment (e.g., chemotherapy, radiation, or endocrine therapy) had shorter overall survival than those with adjuvant treatment delay ≤ 4 months (cumulative survival of 72.6% from delays > 4 months vs. 80.9% for delays ≤ 4 months; p = .041). Also, for each month of delay from surgery to the first adjuvant treatment, the risk of death increases 1.3-fold (HR = 1.35; 95% CI: 1.06–1.71; p = .015). Additionally, using data from the California Cancer Registry, Chavez-MacGregor, Clarke, Lichtensztajn, and Giordano (2016) evaluated the determinants in delayed chemotherapy initiation and the relationship between time to chemotherapy and survival outcomes in a large population-based cohort of 24,843 patients with invasive (stage I–III) breast cancer. Patients who initiated first dose of chemotherapy ≥ 91 days after surgery had a 34% increase in the risk of death (HR = 1.34; 95% CI: 1.15–1.57) and a 27% increase in the risk of breast cancer death (HR = 1.27; 95% CI: 1.05–1.53) compared with patients receiving chemotherapy within 31 days from surgery. In a large retrospective study of 6,827 women diagnosed with stage I–III breast cancer who received adjuvant chemotherapy, Gagliato et al. (2014) found that delaying initiation of adjuvant chemotherapy > 60 days after surgery influenced overall survival for breast cancer patients with known factors for worse prognosis, including patients with stage II breast cancer (HR = 1.20; 95% CI: 1.02–1.43), stage III breast cancer (HR = 1.76; 95% CI: 1.26–2.46), triple negative breast cancer (HR = 1.54; 95% CI:1.09 –2.18), and trastuzumab–treated–HER+ tumors (HR = 3.09; 95% CI: 1.49–6.39) compared with those who initiated

adjuvant chemotherapy within 30 days from surgery. Among patients diagnosed with early-stage breast cancer (stage I or II), adjuvant chemotherapy delays > 3 months from surgery have also been associated with increased disease-specific (HR = 1.69; 95% CI: 1.31–2.19) and overall (HR = 1.46; 95% CI: 1.21–1.75) mortality compared with those who initiated adjuvant chemotherapy within one month of surgery (Hershman et al., 2006b), as well as lower overall survival (HR = 1.6; 95% CI: 1.2–2.3; p = .005) compared with adjuvant chemotherapy treatment delays ≤ 3 months from surgery (Lohrisch et al., 2006).

1.5 Factors Associated with Breast Cancer Treatment Delays

Previous research has evaluated a number of patient demographic characteristics, including race/ethnicity, health insurance, income, and age, as well as medical, environmental, and health system characteristics associated with delays in initiation of breast cancer treatment.

Race/Ethnicity. Numerous studies have demonstrated that African American and Hispanic women have a higher risk of experiencing delays in breast cancer treatment initiation compared to White women (e.g., Ashing-Giwa et al., 2010; Bleicher et al., 2016; Bleicher et al., 2012; Elmore et al., 2005; Fedewa et al., 2011; Fedewa, Ward, Stewart, & Edge, 2010; Gorin et al., 2006; Gwyn et al., 2004; Lund et al., 2008; McGee, Durham, Tse, & Millikan, 2013; Smith, E. C. et al., 2013), which have been associated with poorer outcomes and increased mortality (Hershman et al., 2006b; Hershman & Xiaoyan, 2006; Richards, Westcombe, Love, Littlejohns, & Ramirez, 1999). For example, McGee et al. (2013) evaluated breast cancer treatment delays in the population-based Carolina Breast Cancer Study of North Carolina women and found that African American women were more than three times as likely to experience treatment delay (> 30 days from diagnosis) than White

women for younger age groups, specifically, women 20–39 years old (OR = 3.34; 95% CI: 1.07–10.38) and women 40–49 years old (OR = 3.40; 95% CI: 1.76–6.54). Other studies have found that, compared with White women, African American women were significantly more likely to report longer treatment delays from breast cancer diagnosis ($P = .004$; Ashing-Giwa et al., 2010), with a greater median time (23 days vs. 18 days; $P = .0001$) from diagnosis to treatment initiation (Elmore et al., 2005). African American women also have a 1.64-fold (95% CI: 1.40-1.91; Gorin et al., 2006) or a 4.72-fold (95%: 2.86–7.78; Gwyn et al., 2004) increased odds of experiencing treatment delay beyond one month from diagnosis, and were 4-5 fold more likely to experience treatment delays greater than 60 days ($P < .001$) regardless of stage (Lund et al., 2008) when compared to White women.

African American and Hispanic women also experience greater treatment delays in surgical treatment for breast cancer compared to White women (Bilimoria et al., 2011; Bustami, Shulkin, O'Donnell, & Whitman, 2014; McGee et al., 2013; Mosunjac et al., 2012; Pocock et al., 2007; Sheppard et al., 2015; Smith, E. C. et al., 2013). For example, Bleicher et al. (2012) used SEER–Medicare linked databases to evaluate preoperative delays between first physician visit and first therapeutic surgery among 72,586 participants diagnosed with stage I-III breast cancers, and found that African American and Hispanic women (each 37 days; $P < .001$) had a greater median surgical delay compared to White women (28.6 days). Other studies have similarly reported that African American (OR = 1.68; 95% CI: 1.63-1.73) and Hispanic (OR = 1.83; 95% CI: 1.76-1.91) breast cancer patients were more likely to experience surgery delays ≥ 30 days from diagnosis than White patients (Bilimoria et al., 2011), and African American women were more likely to have longer median times to surgery from diagnosis (34 vs. 28 days; $p = .019$) (Bustami et al., 2014) and 58% less likely to

receive surgery before 90 days (HR = 0.58; 95% CI: 0.44–0.78) compared to White women, after controlling for clinical, process, and psychosocial factors (Sheppard et al., 2015). In Mosunjac et al.'s (2012) study comparing time to treatment among 270 female patients receiving BCS from two different hospital settings (public vs. private), three consecutive treatment time intervals were evaluated (abnormal imaging to core biopsy, biopsy to surgery with pathologic staging, and then surgery to oncology evaluation for adjuvant treatment), and timely treatment was defined as the receipt of each treatment interval within 30 days or the overall spectrum of care (from abnormal imaging to oncology adjuvant treatment) within 90 days. African American women experienced longer median times for the overall spectrum of treatment than White women (89 vs. 64 days; $p = .003$), while White women (OR = 3.8; 95% CI: 1.3–11.5) were the most likely to receive oncology adjuvant treatment within 30 days of surgery, followed by those with Medicare (OR = 2.9; 95% CI: 1.2–7.1) and private (OR = 2.5; 95% CI: 1.1–5.6) insurance. Among young women (aged 15–39 years) with breast cancer, a retrospective case study of 8,860 breast cancer cases found African American and Hispanic women with public or no insurance and low socioeconomic status (SES) were more likely to have longer treatment delay (> 6 weeks) from diagnosis to surgical treatment compared to White women and those privately insured and of higher SES (Smith, E. C. et al., 2013).

Following surgery, research similarly indicates that African American and Hispanic women with breast cancer experience greater delays in initiation of adjuvant treatment. In a population-based analysis of Medicare-eligible women (age 65 years and older) with breast cancer, Freedman, He, Winer, and Keating (2013) found that African American women had higher odds (OR = 1.25, 95% CI: 1.10–1.42) of adjuvant treatment delays, defined as receipt of first chemotherapy or radiation therapy > 90 days after breast surgery, compared to White

women. In another population-based study of 24,843 patients with invasive (stage I–III) breast cancer from the California Cancer Registry, African American (OR = 1.38; 95% CI: 1.19–1.60) and Hispanic (OR = 1.15; 95% CI: 1.03–1.29) women were significantly more likely to experience delays in initiation of adjuvant chemotherapy (≥ 91 days) after surgery compared with White women (Chavez-MacGregor et al., 2016). A national cohort study on women with invasive breast cancer reported that African American and Hispanic women had higher risks of 60-day (RR = 1.36; 95% CI: 1.30–1.41 and RR = 1.31; 95% CI: 1.23–1.39, respectively) and 90-day (RR = 1.56; 95% CI: 1.44–1.69 and RR = 1.41; 95% CI: 1.26–1.59, respectively) adjuvant chemotherapy delay after biopsy compared with White patients, independent of health insurance status, cancer stage, and age (Fedewa et al., 2010). Additionally, Gold et al. (2009) reported that African American women were more likely to delay initiation of radiotherapy (> 8 weeks) after surgery compared to White women (OR = 1.56; 95% CI: 1.17–2.08).

Although most studies have found African American and/or Hispanic women were more likely to experience treatment delays than White women, not all studies have found significant racial/ethnic differences in the timely initiation of breast cancer treatment (Gregorio, Cummings, & Michalek, 1983; Hershman et al., 2006a, 2006b; Jung et al., 2011; Parsons et al., 2015; Smith, E. R. et al., 2008; Williams, D. L., Tortu, & Thomson, 2010). Several studies using SEER–Medicare linked data found no significant racial/ethnic differences in chemotherapy delays after surgery (> 3 months; Hershman et al., 2006b) or diagnosis (> 4 months; Wheeler et al., 2012a), or in radiotherapy delays after surgery (> 3 months; Hershman et al., 2006a). In addition, a retrospective study of 362 female breast cancer patients at a National Cancer Institute (NCI)–designated cancer comprehensive center

in San Antonio, Texas, which serves a majority Hispanic population, found that Hispanic and non-Hispanic White women had similar times from biopsy to treatment initiation (HR = 1.13; 95% CI, 0.69–1.88; Parsons et al., 2015). The authors suggested that racial/ethnic disparities might be attenuated in settings where racial/ethnic minorities represent a majority of the population and patients receive care from large cancer centers.

Income and Health Insurance. In general, people with lower socioeconomic status (SES) have higher cancer mortality rates than those with higher SES, regardless of race/ethnicity or other demographic factors (American Cancer Society, 2016a, 2018). Those of lower SES experience greater cancer burden and significant barriers to care, and generally also have higher cancer incidence rates (American Cancer Society, 2016a, 2018). Lower SES has been associated with multiple risks factors for cancer, including unhealthy lifestyle behaviors (e.g., poorer dietary habits, less physical activity, and smoking) and environmental exposures (e.g., carcinogens, air or water pollutants), as well as limited access to cancer care (Bigby & Holmes, 2005; Brody & Rudel, 2003; Byers et al., 2008; Cross, Harris, & Recht, 2002; Lee, R. E. & Cubbin, 2002). Racial/ethnic minorities are much more likely to be uninsured than non-Hispanic whites (Ward et al., 2008) and to have lower income. In 2015, 11.1% of African Americans and 16.2% of Hispanics were uninsured compared to 6.7% of non-Hispanic whites (Barnett & Vornovitsky, 2016). Additionally, in 2015, 24.1% of African Americans and 21.4% of Hispanics lived in poverty, compared to 9.1% of non-Hispanic whites (Proctor, Semega, & Kollar, 2016).

A person's SES also affects one's ability to obtain health care, and so women with low SES tend to not receive a wide range of health care services. Patients with Medicaid or without insurance are less likely to receive definitive surgery and/or radiation therapy for

cancer, and have much worse survival rates (Niu, Roche, Pawlish, & Henry, 2013; Walker et al., 2014). Studies have also demonstrated that patients with low income and with public (e.g., Medicaid, Medicare) or no insurance were more likely to have longer wait times for surgery (Gwyn et al., 2004; Smith, E. C. et al., 2013) and adjuvant treatments (Fedewa et al., 2010; Freedman et al., 2013; Wheeler et al., 2012a) compared to higher income or privately insured patients. In a large population-based study of 24,843 invasive (stage I–III) breast cancer patients, low SES (OR = 1.40; 95% CI: 1.21–1.62), non-private insurance—Medicaid (OR = 2.19; 95% CI: 1.97–2.43) or Medicare (OR = 1.53; 95% CI: 1.30–1.82), and lack of insurance (OR = 1.66; 95% CI: 1.13–2.43) were significant factors associated with delays in initiation of adjuvant chemotherapy (> 91 days) from surgery (Chavez-MacGregor et al., 2016). In another large study of 107,587 breast cancer patients, insurance was an independent factor in predicting adjuvant chemotherapy delays from biopsy, as those who were uninsured (RR = 1.49; 95% CI: 1.39-1.60; RR = 1.62; 95% CI: 1.41-1.87), Medicaid insured (RR = 1.55; 95% CI: 1.48-1.63; RR = 1.81; 95% CI: 1.65-1.99), and younger Medicare insured (RR = 1.35; 95% CI: 1.26-1.45; RR = 1.74; 95% CI: 1.53-1.98) patients had higher rates of 60- and 90-day delays compared with privately insured patients (Fedewa et al., 2010). Among young (< 40 years) breast cancer patients, those with low SES and with public or no insurance had more surgical treatment delays (> 6 weeks) from diagnosis than those with high SES (17.5% vs. 7.7%; $p < .001$) and with private insurance (17.8% vs. 9.5%; $p < .001$), respectively (Smith, E. C. et al., 2013). Similarly, Bilimoria et al. (2011) reported that breast cancer patients with Medicaid or without insurance were more likely to have longer wait times for surgery. Wheeler et al. (2012a) used SEER–Medicare linked data to examine the receipt and timing of initiation of adjuvant chemotherapy among 6,678 Medicare-enrolled women diagnosed with

stage II or III hormone receptor-negative breast cancer, for which adjuvant chemotherapy is guideline-recommended, but the overall uptake of adjuvant chemotherapy was low (43%). Although everyone in this sample was Medicare-insured, low-income status was significantly associated with lower odds of adjuvant chemotherapy initiation within 4 months of diagnosis ("timely initiation" based on NCCN quality metrics; Desch et al., 2008) among patients aged 65–69 years (OR = 0.49; 95% CI: (0.33–0.72) and 70 years and older (OR = 0.59; 95% CI: 0.48–0.73).

Age. A woman's risk of developing breast cancer increases as she gets older. In fact, age is the strongest risk factor for this disease. Women in the United States who are 70 years old have a 3.9%, or 1 in 25, lifetime risk of developing invasive breast cancer in the next 10 years compared to a 2.3% (1 in 43) or a 3.4% (1 in 29) lifetime risk for women who are 50 or 60 years old, respectively (American Cancer Society, 2017). Older aged women are also more likely to present with advanced stages of breast cancer, when treatments are generally less effective, and are less likely to receive standard or aggressive treatments compared with younger breast cancer patients (Du, X., Freeman, & Goodwin, 1999; Gennari et al., 2004; Tesarova, 2013).

Studies have also demonstrated that older age is associated with longer treatment delays. Two population-based studies using SEER-Medicare data found that compared to 65-69 year old patients, those who were 80 years and older had a 6.7-fold increased risk (OR = 6.7; 95% CI: 4.9–9.2) of delaying adjuvant chemotherapy (Hershman et al., 2006b) or a 1.5-fold increased risk (OR = 1.48; 95% CI: 1.11–1.87) of delaying radiation therapy (Hershman et al., 2006a) longer than 3 months. Additionally, two other population-based analyses of Medicare-eligible women (age 65 years and older) found that older breast cancer patients (>

71 years) had higher risk of adjuvant chemotherapy or radiation therapy delay > 90 days from surgery (OR = 1.10, 95% CI: 1.01–1.21 [age 71–75]; OR = 1.30, 95% CI: 1.17–1.44 [age 76–80]; OR = 1.92, 95% CI: 1.73–2.14 [age >80]) compared to women aged 66–70 (Freedman et al., 2013), and increasing age was significantly ($p < .01$) associated with lower odds of chemotherapy initiation within or equal to four months of diagnosis among women aged 70 and older (Wheeler et al., 2012a). Similarly, a large national cohort study of 107,587 breast cancer patients found that patients 70 years and older were much more likely to experience adjuvant chemotherapy delays, with patients aged 80–99 years having the highest risk of 60-day (OR = 1.64; 95% CI: 1.44–186) and 90-day (OR = 1.71; 95% CI: 1.34–2.17) delays from biopsy compared to younger (18-49 years old) patients (Fedewa et al., 2010). In a smaller study of 238 breast cancer patients in an urban safety net hospital in Louisiana, increasing age was the only risk factor for treatment delay (> 60 days from diagnosis), such that the odds of experiencing a delay increased 1.6 times (OR = 1.6; 95% CI: 1.12–2.26) for every 10-year increase in age (Williams, D. L. et al., 2010). Additionally, older age was significantly ($p = .002$) associated with increased time from imaging to surgery (Wagner et al., 2011) among 818 breast cancer patients from the University of Texas M. D. Anderson Cancer Center.

Comorbid conditions, lower functional status, reduced mobility, less support, and worse general health, all of which are associated with older age, may play a role in preventing or delaying older patients from receiving recommended breast cancer treatments. The presence of comorbidities increases dramatically with age, such that 80- to 89-year old patients have an average of five serious comorbidities, while 50- to 59-year old patients have an average of one or two serious comorbidities (Yancik et al., 2001), and the usual recommended breast cancer treatments can be complicated by comorbidities (Dehal, Abbas,

& Johna, 2013; Lee, L., Cheung, Atkinson, & Krzyzanowska, 2011; Sasaki et al., 2013; Srokowski, Fang, Hortobagyi, & Giordano, 2009). For example, older breast cancer patients who have diabetes have an increased risk of chemotherapy-related toxicities and a higher all-cause mortality compared with non-diabetic patients (Srokowski et al., 2009). Furthermore, guidelines for standard breast cancer treatment have been developed from randomized controlled trials (RCTs) that frequently exclude older patients (> 70 years) and those with comorbidities (Fortin et al., 2006; Lewis et al., 2003), and so the lack of established breast cancer treatment guidelines for older patients with and without comorbidities further complicates treatment decisions, which may in turn contribute to observed treatment delays.

Medical Comorbidities. Comorbidities or coexisting illnesses, such as diabetes, chronic obstructive pulmonary disease (COPD), and high blood pressure, independently shorten life expectancy, and the addition of cancer can further impact survival outcomes. Comorbidity in breast cancer patients contributes more to higher overall mortality than to breast cancer-specific morality (Maskarinec, Sen, Koga, & Conroy, 2011; Tammemagi, Nerenz, Neslund-Dudas, Feldkamp, & Nathanson, 2005). Comorbidities and cancer often co-occur because they share the same risk factors (e.g., obesity, poor diet, lack of physical activity, smoking, and alcohol abuse), and the biological mechanisms associated with comorbidity may predispose patients to cancer (American Cancer Society, 2016a, 2018; Extermann, 2007). Racial/ethnic minorities and people with lower income tend to have a higher prevalence of comorbidity with cancer (Louwman et al., 2010; Meyer, Yoon, & Kaufmann, 2013; Sarfati, Koczwara, & Jackson, 2016). Previous research has shown that patients with comorbidities generally receive less treatment than recommended by guidelines (Janssen-Heijnen et al., 2005; Land, Dalton, Jensen, & Ewertz, 2012; Lee, L. et al., 2011;

Maskarinec et al., 2011), and have lower breast cancer survival rates (Maskarinec, Pagano, Yamashiro, & Issell, 2003; Maskarinec et al., 2011; Satariano & Ragland, 1994) compared to patients without comorbidities.

Greater number of comorbidities has also been linked with breast cancer treatment delays (Bilimoria et al., 2011; Fedewa et al., 2011; Fedewa et al., 2010; Freedman et al., 2013; Hershman et al., 2006a; Wheeler et al., 2012a). For example, Freedman et al. (2013) found breast cancer patients with more than two comorbidities have an increased risk of adjuvant treatment delay (> 90 days from surgery) compared to patients without comorbidities (OR = 1.70; 95% CI: 1.51–1.92), and Wheeler et al. (2012a) found that among breast cancer patients aged 70 and older, greater co-morbidity was significantly ($p < .01$) associated with lower odds of initiating chemotherapy within four months of diagnosis. Breast cancer patients who have two or more medical comorbidities are more likely to experience greater surgery delays (≥ 30 days) from diagnosis (OR = 1.17; 95% CI: 1.14–1.20; Bilimoria et al., 2011) and adjuvant radiotherapy delays ≥ 3 months following BCS (OR = 2.06; 95% CI: 1.56-2.72; Hershman et al., 2006a), as well as have increased risk of 30-day (RRs = 1.10 95% CI: 1.07-1.13), 60-day (RR = 1.29 95% CI: 1.20-1.37) 90-day (RR = 1.29 95% CI: 1.15-1.44) breast cancer treatment delay from biopsy (Fedewa et al., 2011), and 60-day (RR = 1.32; 95% CI: 1.21–1.45) and 90-day (RR = 1.32; 95% CI: 1.10–1.60) adjuvant chemotherapy delay from BCS (Fedewa et al., 2010) compared to patients who have no comorbidities.

Comorbidities can complicate the usual recommended treatments for breast cancer (Lee, L. et al., 2011) and result in higher rates of complications after breast cancer surgery (Dehal et al., 2013) and increased risk of chemotherapy-related toxicities (Sasaki et al., 2013; Srokowski et al., 2009), particularly among breast cancer patients who also have diabetes

(Srokowski et al., 2009). Drug interactions may also occur between medications for comorbidities and chemotherapeutic agents, which may result in increased toxicity, decreased effectiveness of therapeutic regimen, and reduced compliance (Beijnen & Schellens, 2004; Blower, de Wit, Goodin, & Aapro, 2005; Riechelmann & Del Giglio, 2009; Sasaki et al., 2013). Additionally, some breast cancer treatments may impact or worsen comorbidity outcomes. For example, anti-HER2 therapies have been associated with development of cardiac failure (Smith, L. A. et al., 2010) and hormonal treatments for breast cancer have been associated with greater likelihood and severity of osteoporosis (Lustberg, Reinbolt, & Shapiro, 2012). Furthermore, similar to older age, there is substantial inconsistency in cancer treatment decisions based on comorbidities, which likely reflects the general lack of high-level evidence relating to breast cancer treatments for patients with comorbidities (Fortin et al., 2006; Lewis et al., 2003; Muss, 2010; Sarfati et al., 2016).

Family History of Cancer. While most women who get breast cancer do not have a family history of the disease, a woman's risk of breast cancer nearly doubles if she has a first-degree relative (i.e., mother, sister, or daughter) who has been diagnosed with breast cancer, and her risk increases with more affected first-degree relatives (American Cancer Society, 2018). In a multinational analysis of delays in breast cancer diagnosis and treatments across 12 countries, having a family history of female cancers was associated with shorter treatment delays, indicating that the health care system may respond more rapidly to women with a higher risk of breast cancer (Jassem et al., 2014). On the contrary, among 380 women in a population-based study in Germany, family history of breast cancer (OR = 2.5; 95% CI: 1.1–5.5) was associated with greater provider delay, defined as 1–3 months or > 3 months from first consultation (date of presenting the symptom to the doctor or abnormal screening) to start

of treatment (Arndt et al., 2003). Moreover, in two other studies, family history of breast cancer was not significantly associated with timely initiation (< 30 days) of breast cancer treatment (e.g., surgery, neoadjuvant chemotherapy, chemotherapy, hormonal therapy) from diagnosis among 950 African American and White women aged 20-54 (Gwyn et al., 2004) or 771 African American and White women aged 20-74 (McGee et al., 2013) who were diagnosed with invasive breast cancer. Additional studies are needed to further examine the effect of family history of cancer on timeliness of breast cancer treatment initiation.

Geographic Residence. Women living in rural or isolated areas face substantial barriers to accessing health care, and consequently utilize cancer care less frequently (Douthit, Kiv, Dwolatzky, & Biswas, 2015; Higginbotham, Moulder, & Currier, 2001). Patients living in rural regions often have to travel greater distances between medical facilities and have fewer health services available to them. A recent meta-analysis of disparities in breast cancer stage at diagnosis in urban and rural adults found that rural breast cancer patients were more likely to be diagnosed with more advanced breast cancers, and have 1.19 higher odds (95% CI: 1.12-1.27) of late stage breast cancer compared to urban breast cancer patients (Nguyen-Pham, Leung, & McLaughlin, 2014). Rural women also have difficulty obtaining breast cancer treatment services, which may contribute to studies showing that women residing in rural areas are significantly less likely to receive radiation and radiation plus surgery for breast cancer (OR = 0.59; p = .0001) and BCS (OR = 0.73; p = .005) than urban patients (Markossian & Hines, 2012). Rural patients are also less likely to receive radiotherapy (OR = 0.83; 95% CI: 0.71–0.96) but are more likely to receive surgery (OR = 1.30, 95% CI: 1.06–1.60) (Markossian, Hines, & Bayakly, 2014). Rural patients may receive more surgery

because it requires fewer follow-up visits, and may receive less adjuvant therapy because it requires more frequent visits to the provider.

Studies have also found that rural breast cancer patients have higher risk of breast cancer treatment delay. A population-based study of 54,592 Medicare-eligible women (> 65 years) found that breast cancer patients residing in rural areas (OR = 1.79; 95% CI: 1.26–2.54) had higher odds of adjuvant treatment delay (> 90 days from surgery) compared to patients from major metropolitan areas (Freedman et al., 2013). Gorin et al. (2006) also evaluated delays in initiation of breast cancer treatment (definitive surgery, neoadjuvant chemotherapy or radiation, or chemotherapy or hormonal therapy for metastatic disease) beyond 1 month of diagnosis among 49,865 female SEER-Medicare enrollees diagnosed with breast cancer, but found patients residing in the most rural areas (population of city ≤ 19,999) experienced 68% of the odds of treatment delay (OR = 0.68; 95% CI: 0.58–0.80) of women in large metropolitan cities. Two other studies using SEER-Medicare data found living outside of metropolitan areas was significantly ($p < .01$) associated with increased likelihood of adjuvant chemotherapy delay (OR = 1.15; 95% CI: 1.1–2.1; Hershman et al., 2006b) or adjuvant radiotherapy delay (OR = 1.48; 95% CI: 1.00–2.19; Hershman et al., 2006a) longer than three months after surgery compared to patients residing in metropolitan areas. However, these two studies did not define what constituted a metropolitan area, although it commonly refers to a region consisting of a densely populated urban core with a population size larger than urban areas.

Health System. Increasing evidence suggests that the hospitals where patients receive care may influence racial disparities in breast cancer outcomes, including the receipt of breast cancer treatment and breast cancer mortality (Breslin et al., 2009; Keating, Kouri, He, Weeks,

& Winer, 2009). Racial/ethnic minorities, those living in rural areas, and those with lower socioeconomic status are more likely to receive breast cancer care at low-volume hospitals (e.g., performing < 20 surgeries a year to treat breast cancer; Kong et al., 2011), which have been shown to perform fewer breast cancer surgeies and radiation treatments (Bailie, Dobie, Kirk, & Donnelly, 2007; Guller et al., 2005). This decentralization of care creates additional barriers to accessing timely and quality care. Studies have also demonstrated that structural/organizational characeristics of health care systems (e.g., distance to facility, facility size/volume, type of facility, services available onsite) may impact timeliness of breast cancer treatment initiation. Using SEER-Medicare data, Wheeler et al. (2012b) evaluated the effects of health system factors on timing of guideline-concordant initaition of radiation therapy among 38,574 women (> 65 years old) diagnosed with stage I–III breast cancer who received BCS. Attending a for-profit/private surgical facility (OR = 1.35; $p < .01$), facility with on-site radiation services (OR = 1.35; $p < .01$), and smaller facility with fewer beds (< median; OR = 1.08; $p < .05$) were all signifiantly associated with higher odds of initiation of radiation therapy within two months of diagnosis. On the other hand, attending a NCI-designated Comprehensive Cancer Center (OR = 0.57; $p < .01$) or government-owned facility (OR = 0.89; $p < .05$) was associated with significantly lower odds of initiation of radiation therapy within two months of diagnosis. In contrast, when evaluating timeliness of adjuvant chemotherapy initiation among 20,898 female Medicare-enrollees diagnosed with hormone receptor-negative stage II or III breast cancer, health system factors, including surgicial facility type/ownership, distance traveled to facility, and facility size, were not predictive of initiation of adjuvant chemotherapy within four months of diagnosis (Wheeler et al., 2012a).

Two other studies using data from the NCDB found health system factors (i.e., treatment facility type, volume of breast cancer patients) were significantly associated with breast cancer treatment delays among 107,587 women diagnosed with stage I-III breast cancer who were treated with surgery and adjuvant chemotherapy (Fedewa et al., 2010) and among 250,007 women diagnosed with stage I-III breast cancer who received initial treatment for breast cancer (i.e., surgery, chemotherapy, radiation, and/or hormone therapy) after biopsy (Fedewa et al., 2011). Specifically, women treated at teaching/research and NCI-designated Cancer Centers had a higher risk of 60-day (OR = 1.39; 95% CI : 1.31–1.47, and OR = 1.60; 95% CI: 1.49–1.73, respectively) and 90-day (OR = 1.29; 95% CI : 1.16–1.44, and OR = 1.24; 95% CI: 1.06–1.46, respectively) adjuvant chemotherapy delay from surgery compared to those treated at community cancer centers (Fedewa et al., 2010). Additionally, women treated at low-volume (1-137 breast cancer patients treated during study period) and medium-volume (138-288 breast cancer patients treated during study period) facilities also had an increased risk of 60-day (OR = 1.28; 95% CI : 1.21–1.36, and OR = 1.15; 95% CI: 1.11–1.19, respectively) and 90-day (OR = 1.21; 95% CI : 1.08–1.37, and OR = 1.19; 95% CI: 1.11–1.28, respectively) adjuvant chemotherapy delay compared to those treated at high-volume facilities (289-1,789 breast cancer patients treated during study period; Fedewa et al., 2010). When breast cancer treatments were combined, patients treated at teaching/research centers had higher risk of 30-day (RR = 1.29; 95% CI : 1.27–1.32), 60-day (RR = 1.47; 95% CI : 1.40–1.54), and 90-day (RR = 1.38; 95% CI : 1.28–1.49) treatment delay from biopsy compared to those treated at community cancer centers, and patients treated at comprehensive community cancer centers had a modest, but significantly higher risk of 30-day (RR = 1.09; 95% CI :

0.94–1.11) and 60-day (RR = 1.10; 95% CI : 1.050–1.15) treatment delay from biopsy compared to those treated at community cancer centers (Fedewa et al., 2011).

Studies have also used area-level measures of availabilty of cancer care services by evaluating the number of hospitals that offer oncology or radiation services, and specific breast cancer care services (Halpern & Holden, 2012), or the number of breast cancer treating physicians, including general surgeons and radiation oncologists, available in the patient's county of residence (Markossian et al., 2014). However, both studies found these area-level measures of cancer care access were not significantly associated with breast cancer treatment outcomes, and have noted the limitations of measuring access to cancer care services at the county level. Measuring availability of cancer care services at each facility provides a more precise measure of a patient's access to services, which may produce more significant findings regarding its effect on timeliness of treatment initiation.

1.6 Summary and Limitations of Prior Research

Prior research evaluating timeliness of breast cancer treatment has identified multiple patient characteristics, including race/ethnicity, age, income, health insurance, medical comorbidities, family history of cancer, and geographic residency, as well as health care facility characteristics, including facility type, size/volume, institutional affiliations, and type of cancer-related services available onsite, that contribute to treatment delays. Of all the studies that have examined correlates and predictors of timeliness to breast cancer treatment initiation, few have conducted multivariate analyses evaluating multiple patient characteristics in addition to structural/organizational factors in health care delivery. Notably, based on data from large population-based and national hospital-based cancer registries, five studies used multivariate-adjusted models and demonstrated that African American and Hispanic patients,

increasing age, higher comorbidity burden, lack of or public insurance, and low-income status, as well as patients treated at teaching/research facilities, NCI-designated cancer centers, comprehensive community cancer centers, government-owned facilities, Veterans' Affairs institutions, or low- and medium-volume facilities were significantly associated with greater delays in treatment initiation (Bilimoria et al., 2011; Fedewa et al., 2011; Fedewa et al., 2010; Wheeler et al., 2012a, 2012b). While a growing number of studies have identified several factors associated with timely initiation of breast cancer treatment, no study has developed specific typologies of breast cancer patients based on simultaneous evaluation of patient demographic, medical, environmental, and health system factors to evaluate how multiple individual and contextual factors synergistically impact timeliness of breast cancer treatment initiation. Rather than evaluating how individual factors relate to timely initiation of breast cancer treatment, this approach would expand on current literature and provide a deeper understanding of how these factors are interrelated and simultaneously contribute to breast cancer treatment delays. This improved comprehension may also further elucidate the complexities of breast cancer disparities and how or why certain subgroups, not just racial/ethnic minorities, experience greater disparate outcomes.

1.7 Present Study

The present study aimed to identify subgroups of breast cancer patients based on multiple individual and contextual factors associated with timeliness of breast cancer care, and evaluate whether the emergent classes predicted timely initiation of breast cancer treatment. This study investigated the following Specific Aims:

Specific Aim 1: The first aim was to identify subgroups (latent classes) of breast cancer patients based on demographic, medical, environmental, and health system factors that

have been individually shown to influence timely initiation of breast cancer treatment. Latent class analysis (LCA) was used to analyze relations among eight indicators representing individual and contextual factors associated with timeliness of breast cancer treatment initiation and derive distinct classes of patients who display similar patterns of characteristics. Since LCA is exploratory in nature, hypotheses regarding the number or defining characteristics of classes that would emerge could not be made. However, it was hypothesized that multiple groups of breast cancer patients would emerge with varying combinations of individual characteristics, including age, race/ethnicity, annual household income, health insurance coverage, medical comorbidities, and family history of cancer, and contextual characteristics, including urban/rural geographic residence and health system factors, specifically, availability of breast cancer related services onsite at the health care facility where patient received care.

Specific Aim 2: The second aim was to empirically examine if the emergent classes of patients (class membership) were associated with timeliness of breast cancer treatment initiation, defined as initiation of any treatment for breast cancer (e.g., surgery, chemotherapy, radiation, endocrine therapy) within 30 or 60 days of diagnosis, controlling for type of treatment (i.e., chemotherapy, surgery, other). Due to the lack of research on typologies of breast cancer patient characteristics with treatment initiation, specific hypotheses about the emergent classes and their relation to timeliness of breast cancer treatment initiation could not be made. However, based on prior research, it was hypothesized that being a racial/ethnic minority (African American and Hispanic women), older age, lower income, lack of health insurance or public insurance, greater comorbidities, no family history of cancer, rural geographic residence, and facilities with less available breast cancer services would be

associated with greater treatment delays, i.e., defined in this study as initiation of breast cancer treatment more than 30 days or more than 60 days after diagnosis of breast cancer.

1.8 Exploratory Analysis of Disease Stage and Tumor Characteristics on Breast Cancer Treatment and Patient Profiles

Stage of cancer may be considered both a predictor and outcome of breast cancer treatment delay. Both treatment choices and clinical prognosis for breast cancer are determined by stage, tumor size, and hormone receptor status (estrogen receptor [ER] positive [ER+] or negative [ER-] status; progesterone receptor [PR] positive [PR+] or negative [PR-] status), and human epidermal growth factor receptor 2 (HER2) status (HER2 positive [HER2+] or negative [HER2-]). Breast cancer treatments include local therapy, such as surgery and radiation therapy, and systemic therapy, like chemotherapy (American Cancer Society, 2017); and the specific treatments recommended will vary by stage of disease and tumor characteristics. Additionally, delays in breast cancer treatment can result in stage progression (advanced stage of breast cancer), potential worsening of disease, and even death (e.g., Bleicher et al., 2016; Chavez-MacGregor et al., 2016; McLaughlin et al., 2012; Richards et al., 1999). In general, prognosis is worse for more advanced stage breast cancers, as well as ER-, PR-, and HER2- ("triple negative") breast cancers. The poor prognosis for triple negative breast cancers occurs because there are no targeted therapies for this subtype. HER2+ enriched breast cancers tend to grow and spread more aggressively than other breast cancers, but the widespread use of HER2+ targeted therapies (i.e., Herceptin) have reversed much of the adverse prognostic impact of HER2 overexpression (American Cancer Society, 2017). Hormone receptor-positive (ER+ and/or PR+) breast cancers tend to be slow growing and less aggressive compared to other subtypes, and are associated with more favorable

prognosis largely due to effective anti-hormonal treatments (American Cancer Society, 2017). Hormone receptor-positive (ER+ and/or PR+) and HER2-positive (HER2+) breast cancers tend to have a higher tumor grade and are more aggressive than HR+/HER2- breast cancers (American Cancer Society, 2017).

The stage of a cancer helps determine how to treat the cancer and estimate how successful treatment might be. There are a few ways to describe the stages of breast cancer. One of the most common system is the TNM system of staging (Edge et al., 2010), which classifies cancers based on their T, N, and M stages: T = Tumor size; N = Lymph Node status (number and location of lymph nodes with cancer); and M = Metastases (whether or not the cancer has spread to other areas of the body). Once the T, N, and M are determined, a stage of 0, IA, IB, IIA IIB, IIIA, IIIB, IIIC, or IV is assigned, with stage 0 being *in situ* (noninvasive form of breast cancer in which abnormal cells replace the normal epithelial cells of the breast ducts), stage I being early stage invasive cancer, and stage IV being the most advanced disease indicating distant metastasis. Stages can also be described as: local—cancer is confined with the breast; regional—cancer has spread away from the breast and lymph nodes are involved; distant—cancer has metastasized and is found in other parts of the body beyond the breast and lymph nodes (Young, Roffers, Ries, Fritz, & Hurlbut, 2001).

Depending on the results from the physical exam and biopsy, additional tests may be needed to help stage the cancer. Determining the stage of breast cancer after diagnosis may involve multiple surgical, pathological, and imaging processes, testing for breast cancer type (invasive ductal; invasive lobular cancer), breast cancer grade (Grade 1, Grade 2, Grade 3), and classifying the tumor based on hormone receptors (ER+, ER-, PR+, PR-) or gene expression (HER2+, HER2-). Consequently, staging may be determined at multiple time

points, and recorded, changed, or updated in patients' medical records as they receive breast cancer care. For example, breast cancer surgery, which removes the cancer from the breast(s), often involves removal of one or more regional lymph nodes to determine if the cancer has spread, which helps stage the disease. Surgery is the main treatment for early stage breast cancer, but for later stage breast cancers surgery is often conducted after neoadjuvant therapy has first been administered to shrink the tumor size. As a result, patients' breast cancer may be staged post-treatment, such as after surgery has determined the disease stage.

In this current dataset, it was unknown when the staging of cancer and tumor characteristics were recorded in patients' medical records, as they may have been recorded before or after patients received breast cancer treatment. Therefore, the present study conducted an exploratory analysis to evaluate disease stage independently from the primary analyses. First, the association between stage of breast cancer (stage I, II, or III) and timely initiation of breast cancer treatment was evaluated using logistic regression analysis, controlling for tumor characteristics (ER status, PR status, and HER2 status). Second, stage of breast cancer was also evaluated in relation to the emergent classes derived from the primary LCA using logistic regression analysis, controlling for tumor characteristics (ER status, PR status, and HER2 status).

Chapter 1 is being prepared in part for publication. This publication will be co-authored Vanessa L. Malcarne, Kristen J. Wells, Georgia Robins Sadler, Scott C. Roesch, and Carrie R. McDonald. The dissertation author was the primary investigator and author of this material.

CHAPTER 2: METHODS

2.1 Participants

The present study used archival data provided by a subset of participants from the control arm of the Patient Navigation Research Project (PNRP; Freund et al., 2008), a five-year clinical trial involving collaboration among 10 health care institutions located across the United States. The sample for this study included 198 patients with newly diagnosed Stage I-III breast cancer who received usual standard of care (control arm) from four PNRP sites (Denver, Colorado; Rochester, New York; San Antonio, Texas; and Tampa, Florida), and who received at least one type of treatment for breast cancer (e.g., surgery, chemotherapy, radiation, anti-hormonal therapy). All participating sites provided care to medically underserved populations, including racial and ethnic minorities, uninsured or publicly insured patients, and low-income individuals (Freund et al., 2008). Participants were eligible for the PNRP if they were 18 years or older and had an abnormal cancer screening or symptom or a new diagnosis of breast, cervical, colorectal, or prostate cancer. Participants who had been diagnosed with cancer but have never received any type of treatment were also eligible for the PNRP study. Exclusion criteria included history of any prior cancer (except non melanoma skin cancer) within the past five years, previous receipt of patient navigation, cognitive impairment, or pregnancy at time of enrollment. Participants were recruited from community health centers or outpatient care settings within and outside of safety-net hospitals. Each PNRP site obtained Institutional Review Board approval before the initiation of the study (Freund et al., 2008).

2.2 Procedures

The PNRP was a multi-site National Cancer Institute- and American Cancer Society-funded clinical trial designed to evaluate the efficacy and cost-effectiveness of patient navigation in improving cancer care among adult patients with abnormal cancer screening results or new diagnoses of breast, cervical, colorectal, or prostate cancer (Freund et al., 2008). The PNRP was conducted from 2005 to 2010 in 10 health care institutions that included diverse community settings. Participating sites employed varied research study designs that included individual randomized clinical trials (RCTs), group-RCTs, and quasi-experimental (QE) studies. Participants were allocated to either the intervention arm, which included patient navigation services, or the control arm, which included usual standard of care, according to each specific site's protocol.

Nine sites contributed to the national PNRP dataset, as the data sharing agreements at the 10th site, which focused solely on American Indian/Alaska Native populations of the northwestern United States, precluded inclusion into the combined dataset. Eight PNRP sites focused on breast cancer, seven of which evaluated the time period from cancer diagnosis to initiation of cancer treatment. Of these, four PNRP sites (Denver, CO, Rochester, NY, San Antonio, TX, and Tampa, FL) collected patients' medical history data, including comorbidities and family history of cancer, in addition to sociodemographic information and health system data. Across sites, standard methods were used to collect and record data, using a standardized data codebook with definitions of all variables, common data elements, and sources for collection (Freund et al., 2008). Trained research assistants conducted standardized chart review of study participants' medical records to abstract clinical outcome data (Freund et al., 2008). Demographic and medical history data were obtained from

participants' self-report or their medical records. Health system data were collected from surveys completed by each participating care center.

The present dissertation project used archival data from four PNRP sites located in Denver, CO, Rochester, NY, San Antonio, TX, and Tampa, FL. Both the Denver (Raich, Whitley, Thorland, Valverde, & Fairclough, 2012) and Rochester (Fiscella et al., 2012) PNRP sites conducted RCTs, and recruited intervention and control participants from a single oncology clinic (Denver) or 11 oncology practices (Rochester). The Tampa PNRP site conducted a cluster RCT and included 12 clinics/care sites, seven of which were randomized to patient navigation and five that were randomized to usual care (Wells et al., 2012). The San Antonio PNRP site used a QE design with nonrandom allocation of study sites into the intervention or control arms, and included five clinics/care sites, two of which served as the intervention clinics and the other three served as the control clinics (Dudley et al., 2012). Most control participants were recruited via medical record abstraction, for which written informed consent was waived.

2.3 Measures

Patient Demographics. Information regarding patient race/ethnicity, age, household income, and health insurance were extracted from participants' medical records, hospital registration data, or self-report surveys (Freund et al., 2008). Participants with missing demographic variables were still included in primary analyses, as latent class analysis allows cases with missing data to still be included in the analysis as long as the missing data are missing at random.

Race/ethnicity. Across all sites, the race/ethnicity variable was coded as: 1) Black/African American; 2) White; 3) Hispanic/Latino; 4) Asian; 5) Native Hawaiian/Pacific

Islander; 6) American Indian/Alaska Native; and 7) Missing. The current study sample did not include any American Indian/Alaska Native participants. Additionally, given the small number of Asian (n = 1) and Native Hawaiian/Pacific Islander (n = 1) participants, the present study evaluated the three predominant race/ethnicity groups and recoded the race/ethnicity variable to: 1) Black/African American; 2) Hispanic/Latino; and 3) White.

Age at breast cancer diagnosis. The patient's age at the time of breast cancer diagnosis was coded on a continuous scale and entered as number of years.

Annual household income. The annual household income variable was coded as: 1) Less than $10,000; 2) $10,000 to $19,999; 3) $20,000 to $29,999; 4) $30,000 to $39,999; 5) $40,000 to $49,999; 6) $50,000 or more; and 7) Chose not to answer. For the purpose of this study, the income variable was collapsed into two categories to ease interpretation and comparison of income levels, and recoded as: 1) Less than $40,000 and 2) $40,000 or more.

Health insurance. The health insurance variable was coded as: 1) Uninsured; 2) Public insurance (e.g., Medicare, Medicaid, other government-sponsored health plan); and 3) Private insurance.

Patient Medical History. Information regarding medical comorbidities and history of cancer in first-degree relatives were extracted from participants' medical records or administered questionnaires (Freund et al., 2008).

Medical comorbidities. The PNRP recorded the number of comorbidities based on the following 15 conditions abstracted from participants' medical records: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease (COPD), connective tissue disease, peptic ulcer disease, mild liver disease, moderate/severe liver disease, diabetes mellitus without

complications, diabetes with complications, hemiplegia or paraplegia, renal disease, and acquired immunodeficiency syndrome (AIDS). The Charlson Comorbidity Index (CCI; Charlson, Pompei, Ales, & MacKenzie, 1987) was used to calculate a total, weighted comorbidity score. The CCI is a method of categorizing comorbidities, which each comorbidity category has an associated weight (from 1 to 6) depending on the adjusted risk of mortality and resource use, and the sum of all weights results in a single comorbidity score. The CCI assigns 1, 2, 3, or 6 points to the following comorbidities: 1 point: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, COPD, connective tissue disease, peptic ulcer disease, mild liver disease, and diabetes mellitus without complications; 2 points: diabetes with complications, hemiplegia or paraplegia, and renal disease; 3 points: moderate/severe liver disease; and 6 points: AIDS. CCI scores range from 0 to 25.

Family history of cancer. This variable was originally assessed as any cancer in first-degree relatives (i.e., biological father, mother, brother, sister, daughter, or son) and coded as: 0) None; 1) One relative; 2) Two relatives; 3) More than two relatives; 4) Don't know/not sure; and 5) Chose not to answer. The family history of cancer variable in the current study was recoded as a dichotomous variable (yes/no) of whether the patient had any first-degree relatives with any cancer, and the "don't know/not sure" and "chose not to answer" were coded as missing.

Patient Environment.

Geographic residence of patient. Participants' zip codes of residence were extracted from their medical records and then categorized as urban or rural using the United States Census Bureau's urban and rural classification (U.S. Census Bureau, 2012). An urban area

represented a developed territory, comprised of a densely settled core of census tracts and/or census blocks that meet minimum population density requirements, and encompassed residential, commercial, and other non-residential urban land uses. To qualify as an urban area, the territory must have encompassed at least 2,500 people, at least 1,500 of which resided outside institutional group quarters. The Census Bureau identified two types of urban areas: 1) Urbanized areas of 50,000 or more people; and 2) Urban clusters of at least 2,500 and less than 50,000 people. Rural areas encompassed all population, housing, and territory not included within an urban area. The geographic residency status variable for this study was coded into two categories: 1) Urban areas (Urbanized areas or Urban clusters) and 2) Rural areas.

Health System Factors. Information about clinics/facilities where participants were enrolled and received care, including availability of cancer-related services onsite, were collected from surveys completed by each participating care center.

Breast cancer related services. Each health care facility provided data about the type of cancer-related services provided directly onsite. The type of services related to breast cancer care included: mammography screening; diagnostic mammography; breast ultrasound; breast surgeon/breast health center/general surgeon who does breast surgery; medical oncologist; and radiation therapy. Each clinic/facility was assigned a numerical value of the number of breast cancer care services provided directly onsite, ranging from 0 to 6.

Breast Cancer Treatment. The initial breast cancer treatment received was categorized into different types of treatments: 1) Chemotherapy; 2) Mastectomy; 3) Lumpectomy; 4) External radiation therapy; 5) Hormone therapy; 6) Biologic therapy; and 7) Multiple types of treatment. The current study combined mastectomy (n = 69) and

lumpectomy (n = 81) into one treatment category labeled "surgery," and due to low numbers, external radiation therapy (n = 4), hormone therapy (n = 1), biological therapy (n = 0), and multiple types of treatment (n = 0) were combined into the "other" treatment category. This breast cancer treatment variable was recoded as: 1) Chemotherapy; 2) Surgery; and 3) Other. The first type of breast cancer treatment received (i.e., chemotherapy, surgery, other treatment) was used as a covariate when evaluating the associations between emergent LCA classes and timely initiation of breast cancer treatment (outcome).

Clinical and Tumor Characteristics. Cancer stage at diagnosis, hormone receptor status, and human epidermal growth factor receptor 2 (HER2) status were extracted from participants' medical records, and these variables were used in the exploratory analyses to evaluate how disease stage and tumor characteristics relate to timely initiation of breast cancer treatment (outcome) and to the emergent classes of breast cancer patients (results from preliminary analyses).

Breast cancer stage. The stage of breast cancer variable was coded as: 1) Stage I; 2) Stage II; and 3) Stage III.

Hormone receptor and HER2 status. Three variables were created from data collected from medical records regarding hormone receptor and HER2 status. Estrogen receptor (ER) status was coded as: 0) Negative (ER-) or 1) Positive (ER+). Progesterone receptor (PR) status was coded as: 0) Negative (PR-) or 1) Positive (PR+). HER2 status was coded as: 0) Negative (HER2-) or 1) Positive (HER2+). These tumor characteristic variables were used as covariates when evaluating the associations between stage at diagnosis and timely breast cancer treatment initiation and emergent latent classes.

Outcome of Interest.

Timely initiation of breast cancer treatment. Accounting for variation in the type of first breast cancer treatment, timely initiation was defined as the initiation of any breast cancer treatment (i.e., chemotherapy, mastectomy, lumpectomy, external radiation therapy, endocrine therapy, or multiple therapies) within 30 or 60 days of definitive diagnosis of breast cancer. Time to treatment was first measured as a continuous variable defined as the number of days from the date a diagnostic test (i.e., excisional biopsy, stereotactic core biopsy, ultrasound-guided core biopsy, core biopsy without imaging guidance, breast MRI, breast ultrasound, diagnostic mammogram, clinical assessment, or type of breast biopsy not specified) was completed that resulted in definitive cancer diagnosis to the date a patient received the first breast cancer treatment (i.e., chemotherapy, mastectomy, lumpectomy, external radiation therapy, or hormone therapy). This variable was recoded as two dichotomous variables (yes/no) of whether patient received initial breast cancer treatment within 30 or 60 days of cancer diagnosis.

The present study used both 30- and 60-day criteria for timely treatment, as there is a general lack of consensus of what cut-off point is most appropriate in the timeliness of breast cancer treatment initiation. Studies that have analyzed the impact of time to treatment from diagnosis on survival have used varied treatment intervals, which may partly explain different study results. For example, McLaughlin et al. (2012) demonstrated that treatment delays > 60 days from diagnosis increased all-cause and breast cancer-specific mortality, after controlling for treatment type, patient sociodemographic, tumor, comorbidity, and setting-of-care characteristics. Other studies that compared treatment initiation ≥ 1 month versus < 1 month from diagnosis found no significant relationship between survival and treatment delay (e.g., McLaughlin et al., 2012; Redondo et al., 2009; Smith, E. R. et al., 2008). McLaughlin et al.

(2012) suggested that the comparison treatment cut points may have been too short to detect a meaningful difference in survival, as in their study they found no significant difference in survival outcomes between patients when comparing time to treatment intervals of 0 to 29 days to 30 to 59 days. Nonetheless, studies evaluating racial/ethnic differences in the timeliness of breast cancer treatment initiation have commonly used the 30-day criteria and found African American women had higher risks of experiencing treatment delays > 30 days from diagnosis (e.g., Gorin et al., 2006; Gwyn et al., 2004; McGee et al., 2013). Although there are no established professional or practice guidelines regarding the time intervals to initiate specific breast cancer treatments, the National Breast and Cervical Cancer Early Detection Program (NBCCEDP), which provides funding to individuals for breast and cervical cancer care, uses a service delivery benchmark of initiation of treatment within 60 days of diagnosis to ensure timely treatment initiation for underserved women screened through their program (Caplan, May, & Richardson, 2000; Richardson et al., 2010). A recent analysis of compliance with the NBCCEDP treatment initiation benchmark showed a median time to treatment interval of 14 days from diagnosis (Richardson et al., 2010).

2.4 Statistical Analyses

This study had two specific aims: Aim 1) To identify subgroups of breast cancer patients based on demographic, medical, environmental, and health system factors that have been individually shown to influence timeliness of breast cancer treatment; and Aim 2) To examine group differences among emergent classes of breast cancer patients in timely initiation of breast cancer treatment.

Latent class analysis (LCA) is a person-centered statistical approach used to identify distinct subgroups (i.e., latent classes) of individuals, within a heterogeneous population,

based on similar patterns of responses to a set of observed indicator variables. Unlike variable-centered approaches (e.g., factor analysis), which focus on relations among variables and identify a taxonomy of variables (set of latent constructs), person-centered methods focus on similarities and differences among individuals in how variables are interrelated and identify typologies (e.g., subgroups) of people based on their patterns of responses to a set of observed indicator variables. The goal of LCA is to ascertain the fewest number of latent classes (e.g., homogeneous groups) that sufficiently explain heterogeneity of relationships between indicator variables within a population, and to maximize the homogeneity within groups and the heterogeneity between groups, such that members of each subgroup are more similar to one another and dissimilar to members of other groups (Roesch, Villodas, & Villodas, 2010). This method utilizes all observations of indicator variables to derive these classes and to estimate the class probabilities for each person, which allows individuals to be classified into the best-fitting class, simultaneously with the overall model (Hill, Degnan, Calkins, & Keane, 2006).

To achieve the first aim, a LCA was conducted to empirically derive categorical latent variables representing subgroups/classes (latent classes) of breast cancer patients with similar characteristics or patterns of demographic (race/ethnicity [African American, Hispanic, or White]; age at diagnosis in years; health insurance status [uninsured, public insurance, or private insurance]; annual household income [< $40,000 or ≥ $40,000 or more]), medical (medical comorbidities [CCI]; family history of cancer [yes/no]), environmental (geographic residence [urban vs. rural]), and health system (number of breast cancer-related services, ranging from 0 to 6) factors associated with timeliness of breast cancer care. The LCA models were estimated using MPlus 7.2 (Muthén & Muthén, 1998-2012). To estimate the model

parameters, the maximum likelihood robust (MLR) estimation procedure in MPlus was used, which is considered a full information maximum likelihood approach to missing data. MLR estimation allows cases with missing data on one or more variables to still be included in the analyses, as it estimates a likelihood function for each individual based on the study variables that are present so that all available data are used. Therefore, model parameters and standard errors are estimated using all observed data from both complete cases and partial cases.

To identify the optimal number of latent classes, a series of LCA models were estimated with increasing number of classes until there was no further improvement in model fit. Models were evaluated using several fit indices, including the Lo-Mendell-Rubin Adjusted Likelihood Ratio Test (LMRT; Lo, Mendell, & Rubin, 2001), Bootstrapped Likelihood Ratio Test (BLRT; Arminger, Stein, & Wittenberg, 1999; McLachlan & Peel, 2004), Akaike Information Criteria (AIC; Akaike, 1974), sample size-adjusted Bayesian Information Criterion (sBIC; Schwarz, 1978), and Entropy (Ramaswamy, DeSarbo, Reibstein, & Robinson, 1993). The LMRT and BLRT are inferential statistical tests that evaluate whether a target model with *k* classes (e.g., 3-class model) improves significantly from a model with *k*-1 classes (e.g., 2-class model). Significant *p*-values ($p < .05$) indicate that adding another class significantly improves model fit and so the *k*-class model is a superior fit; while non-significant *p*-values ($p > .05$) indicate the model with fewer classes (*k*-1 class) has a better fit. The AIC and sBIC are descriptive model fit indices, in which optimal model fit is indicated by smaller AIC and sBIC values. Entropy measures the accuracy of classification of individuals into a latent class given specific model, with entropy values closer to 1 indicating a better fit model. Lastly, to aid the determination of the optimal number of classes, the interpretability and substantive utility of each class were evaluated using two statistical

parameters—class probabilities and item probabilities. Class probabilities refer to the relative size of each latent class (i.e., the proportion of the sample that is represented in each class) (Masyn, 2013; Nylund-Gibson, Ing, & Park, 2013), and item probabilities refer to the probability that members of a specific class would endorse a particular item (Masyn, 2013; McCutcheon, 1987).

To achieve the second aim, the manual three-step approach (Asparouhov & Muthén, 2014; Vermunt, 2010) was used to examine class differences on timely breast cancer treatment initiation, defined as initiation of any breast cancer treatment within 30 or 60 days of diagnosis, controlling for type of initial treatment received (i.e., chemotherapy, surgery, or other). In this three-step estimation procedure, the first step entails estimating the LCA measurement model using only the latent class indicators and determining the best-fitting model. In the second step, the most likely class variable was obtained from the posterior probabilities of the LCA along with the classification uncertainty rate (i.e., measurement error). In the final step, the most likely class variable was used as a latent class indicator variable and the measurement error was fixed and pre-specified to the logit probability values computed in step 2. The auxiliary model was estimated where class membership was the predictor and dichotomous (yes/no) treatment initiation within 30 days or 60 days was the outcome, while controlling for treatment type. This three-step approach is the recommended method for examining predictors and outcomes of latent class membership in mixture models (Asparouhov & Muthén, 2014; Nylund-Gibson et al., 2013; Vermunt, 2010), as it helps insure the emergent latent classes are not unintentionally influenced by the covariates or distal outcomes.

Lastly, an exploratory analysis was conducted to evaluate the relationships between stage of breast cancer and tumor characteristics (ER status, PR status, and HER2 status) with timely initiation of breast cancer treatment and the emergent classes of breast cancer patients derived from the primary LCA. Specifically, two binomial logistic regression analyses were conducted to evaluate if disease stage predicted timely treatment initiation within 30 days or 60 days (dichotomous outcomes), controlling for ER status, PR status, and HER2 status. Lastly, a multinomial logistic regression examined class membership association with disease stage, controlling for tumor characteristics (ER status, PR status, and HER2 status) using the manual three-step approach for including covariates into the latent class model (Asparouhov & Muthén, 2014; Vermunt, 2010).

Chapter 2 is being prepared in part for publication. This publication will be co-authored Vanessa L. Malcarne, Kristen J. Wells, Georgia Robins Sadler, Scott C. Roesch, and Carrie R. McDonald. The dissertation author was the primary investigator and author of this material.

CHAPTER 3: RESULTS

3.1 Sample Characteristics

Sample characteristics are detailed in Table 1. Among this sample of 198 breast cancer patients, 51.5% were non-Hispanic white, 25.3% were Hispanic, and 18.7% were African American, and the average age at diagnosis was 56.56 years (*SD* = 11.35; range: 24-82 years). Most participants had public or private health insurance, had an annual household income less than $40,000, and nearly all lived in an urban area. Patients were mostly diagnosed with stage I or II breast cancer, and more than half had hormone receptor positive and/or HER2 negative breast cancer. Surgery was the most common initial breast cancer treatment, with 41% receiving lumpectomy, 34.8% receiving mastectomy, and 12.6% receiving chemotherapy as the first treatment.

3.2 Determining the Optimal Number of Latent Classes

A series of LCA models were fit to the data starting with a one-class model, and models with classes added iteratively were compared using multiple statistical and descriptive fit indices to determine the optimal number of latent classes (Muthén and Asparouhov, 2006; Nylund et al., 2007). The fit information for the LCA models with one through five latent classes is presented in Table 2. All indicators of model fit (decreased AIC and sBIC, significant LMRT and BLRT, higher entropy) suggested the two-class solution fit better than the one-class solution. The three-class solution was superior to the two-class solution according to the substantially lower AIC and sBIC values, and statistically significant LMRT (p = .0121) and BLRT (p < .0001) values. Although the AIC, sBIC, LMRT, and BLRT suggested that the four-class solution fit better than the three-class solution, the largest relatively decrease in the AIC and sBIC values occurred with the three-class solution and the

Entropy suggested that the three-class solution fit better than the four-class solution. Furthermore, although the five-class solution revealed slightly lower AIC and sBIC values and a statistically significant BLRT value ($p < .0001$), Entropy was lower and the LMRT indicated that it was not significantly different from the four-class solution ($p = .1026$). However, the four-class solution extracted two similar classes of breast cancer patients, separating one of the classes from the three-class solution into two smaller groups but with less clear differentiating characteristics between the two, suggesting that the three-class solution should be accepted. Additionally, analysis indicated that the standard errors of the model parameter estimates might not be trustworthy for some of the parameters, which indicates possible model nonidentification for the four-class solution. Moreover, the Entropy value further established that the three-class solution was the best classification, demonstrating that 99.5% of the sample could be accurately categorized on the basis of their class membership. Therefore, given these findings, the three-class solution was selected as the best fitting model.

3.3 Class Descriptions

The resulting conditional response probabilities (probability of endorsing an indicator given class membership) for categorical indicator variables and conditional response means for continuous indicator variables were used to characterize the classes and substantively interpret the three-class model, and are presented in Table 3. Items with probabilities greater than .50 were considered to be highly endorsed by members of that particular class (Masyn, 2013).

Class 1 represented the largest class and accounted for 74% ($n = 147$) of the sample. This class was comprised of breast cancer patients who had an average age of 56.58 years (*SE*

= 0.88) at diagnosis, an average of 0.26 medical comorbidities (*SE* = 0.04), and received care at health care facilities that provided an average of 5.39 (*SE* = 0.06) breast cancer-related services onsite at their health care facilities out of 6 total available services (i.e., mammography screening, diagnostic mammography, breast ultrasound, breast surgery, medical oncology, and radiation therapy). Breast cancer patients in this class had less medical comorbidities than patients in Class 3 and had more breast cancer-related services available at their health care facilities than patients in Class 2. Members of this class had a higher probability of being White (.62) and having a family history of cancer (.63) than the other classes, as well as having private health insurance (.49), although Class 3 was similar (.44). While members of all three classes were likely to have an annual household income less than $40,000, the probability of having an annual household income greater than $40,000 was .35 in this class, which was notably higher than the other classes. Given the high endorsement of factors associated with timely breast cancer care, as indicated by prior research, Class 1 was labeled as *Protective Factors*.

Class 2 accounted for 21% (*n* = 42) of the sample and represented breast cancer patients with an average age of 54.24 years (*SE* = 2.00) at diagnosis and the least amount of breast cancer-related services (*M* = 0.08; *SE* = 0.06) available onsite at their health care facilities. Members of this class had a higher probability of having public health insurance (.66) and not having a family history of cancer (.66) than the other classes. They also had a low average of 0.38 medical comorbidities (*SE* = 0.13), similar to Class 1, and a moderate probability of being Hispanic (.47), similar to Class 3. Based on these demographic and health system characteristics previously shown to be associated with greater treatment delays, the second class was labeled as *Demographic and Health System Risks Factors*.

Lastly, Class 3 was the smallest class and represented 5% (n = 9) of the sample. This class was comprised of breast cancer patients with the oldest average age of 66.56 years (SE = 3.35) at diagnosis and the greatest number of medical comorbidities (M = 3.99; SE = 0.34), thus this class was labeled as *Medical Risk Factors.* Within this class, members were equally as likely to be Hispanic (.44) or White (.45) and have public health insurance (.44) or private health insurance (.44), and had a similar probability of having or not having a family history of cancer (.56 vs. .44). Breast cancer patients in this class, similar to Class 1, received care at a health care facility that had a greater number of breast cancer-related services (M = 5.33; SE = 0.16) available onsite than patients in Class 2.

3.4 Differences in Time to Treatment Outcomes Across Breast Cancer Patient Classes

The timeliness to treatment initiation outcome used in this study was evaluated as whether any type of breast cancer treatment was initiated within 30 days (coded 1: ≤ 30 days; 0: > 30 days) or within 60 days (coded 1: ≤ 60 days; 0: > 60 days) from definitive diagnosis of breast cancer. For the type of treatment covariate, chemotherapy and other treatment were compared to surgery (reference treatment group). And *Medical Risk Factors* (Class 3) was used as the reference or comparison class. The odds ratio comparing the likelihood of *Protective Factors* (Class 1) to *Medical Risk Factors* (Class 3) and *Demographic and Health System Risks Factors* (Class 2) to *Medical Risk Factors* (Class 3) initiating breast cancer treatment within 30 days and 60 days are presented in Table 4.

Initiation of Treatment within 30 Days. No significant differences emerged between the *Protective Factors* class and the *Medical Risk Factors* class in the likelihood of initiating breast cancer treatment within 30 days of diagnosis (OR = 0.96; p = .19), controlling for type of treatment. There were no statistically significant differences in the likelihood of initiating

chemotherapy versus surgery ([*b* = -0.90 (*SE* = 0.59)], *p* = .13; OR = 0.41, 95% CI: 0.15, 1.07) or other treatment versus surgery as the first treatment for breast cancer ([*b* = -32.13 (*SE* = 0.01)]; OR = 0.01, 95% CI: 0.01, 0.01) within 30 days from diagnosis. Additionally, there were no significant differences between the *Demographic and Health System Risks Factors* class and the *Medical Risk Factors* class in the likelihood of initiating breast cancer treatment within 30 days of diagnosis (OR = 0.69; *p* = .27), controlling for type of treatment. There were also no significant differences in the likelihood of initiating either chemotherapy ([*b* = 1.28 (*SE* = 1.06)], *p* = .23; OR = 3.60, 95% CI: 0.63, 20.48) or other treatment ([*b* = -34.81 (*SE* = 0.01)]; OR = 0.01, 95% CI: 0.01, 0.01) versus surgery as the first treatment for breast cancer within 30 days of diagnosis.

Initiation of Treatment Within 60 Days. There were no statistically significant differences in the likelihood of initiating breast cancer treatment within 60 days of diagnosis between patients in *Protective Factors* and patients in *Medical Risk Factors* (OR = 0.56; *p* = .36) or between patients in *Demographic and Health System Risks Factors* and patients in *Medical Risk Factors* (OR = 0.46; *p* = .41). There were no significant differences between *Protective Factors* and *Medical Risk Factors* in the likelihood of obtaining chemotherapy versus surgery as the first treatment for breast cancer ([*b* = -0.45 (*SE* = 0.53)], *p* = .40; OR = 0.64, 95% CI: 0.27, 1.53) or other treatment versus surgery as the first treatment for breast cancer ([*b* = -983.32 (*SE* = 0.01)]; OR = 0.01, 95% CI: 0.01, 0.01) within 60 days from diagnosis. There were also no significant differences between *Demographic and Health System Risks Factors* and *Medical Risk Factors* for obtaining chemotherapy versus surgery ([*b* = 0.21 (*SE* = 1.26)], *p* = .87; OR = 1.23, 95% CI: 0.16, 9.71) or other treatment versus

surgery ([*b* = -151.31 (*SE* = 0.01); OR = 0.01, 95% CI: 0.01, 0.01) as the first treatment within 60 days from diagnosis.

Average Days to Initiate Treatment from Diagnosis. The relationship between emergent classes and timeliness of breast cancer treatment initiation was further inspected using a continuous time-to-treatment outcome (average number of days to initiate any type of breast cancer treatment from the day of definitive diagnosis of breast cancer; see Table 5). Overall, controlling for type of initial breast cancer treatment, patients in the *Protective Factors* class initiated treatment in 47.12 days (*SE* = 3.46), *Demographic and Health System Risks Factors* in 56.12 days (*SE* = 13.13), and *Medical Risk Factors* in 40.56 days (*SE* = 7.35). The differences between *Protective Factors* and *Demographic and Health System Risks Factors* (*p* = .51), *Protective Factors* and *Medical Risk Factors* (*p* = .42), and *Demographic and Health System Risks Factors* and *Medical Risk Factors* (*p* = .30) were not statistically significant. Among breast cancer patients in the *Protective Factors* class, the mean difference in time-to-treatment was significantly greater for patients initiating other treatment as the first treatment for breast cancer compared to surgery by 29.15 days (*SE* = 3.57; *p* < .001), but not for chemotherapy versus surgery ([*b* = 14.16 (*SE* = 11.84)], *p* = .23). In other words, patients in the *Protective Factors* class initiated surgery in 44.9 mean days (*SD* = 39.61) compared to an average of 74 days for initiating other treatment (i.e., hormone therapy). Similarly, breast cancer patients in the *Demographic and Health System Risk Factors* class had a significantly higher average time-to-treatment of 95 days (*SD* = 24.04) for initiating other treatment (i.e., external radiation) compared to surgery (*M* = 54.24 days; *SD* = 67.31) as the first breast cancer treatment ([*b* = 40.77 (*SE* = 19.89)]; *p* = .04), but not for chemotherapy versus surgery ([*b* = -8.64 (*SE* = 23.47)], *p* = .71). None of the members of *Medical Risk Factors* received

chemotherapy as the first treatment for breast cancer, and there was no statistically significant difference in time-to-treatment for initiating other treatment (i.e., external radiation) compared to surgery ([b = 7.25 (SE = 8.22)], p = .38) within this class.

3.5 Exploratory Analyses: Associations of Disease Stage with Timeliness to Initiate Breast Cancer Treatment and Emergent Classes

Results from the binomial logistic regression analyses indicated that stage of breast cancer did not significantly predict timeliness of breast cancer treatment initiation, controlling for tumor characteristics (see Table 6). Specifically, patients whose cancer was diagnosed as stage I or stage II, as compared to patients whose cancer was diagnosed as stage III, were not any more likely to initiate breast cancer treatment within 30 days or within 60 days from diagnosis, when holding ER status, PR status, and HER2 status constant. However, compared to patients with stage III breast cancers, the average time-to-treatment was significantly shorter for patients with stage I breast cancers ([b = -24.80 (SE = 9.68)], p = .01) and for patients with stage II breast cancers ([b = -24.22 (SE = 9.514)], p = .01), when controlling for ER status, PR status, and HER2 status (see Table 7). On average, patients with stage I and stage II breast cancers initiated breast cancer treatment from diagnosis in 33.45 days (SE = 7.08) and 34.03 days (SE = 6.70), respectively, compared to an average time-to-treatment of 58.21 days (SE = 11.67) for patients with stage III breast cancers. When disease stage and tumor characteristics (ER status, PR status, and HER2 status) were regressed onto class membership, results indicated no significant associations (see Table 8). Specifically, patients diagnosed with stage I or stage II breast cancer, as compared to patients with stage III breast cancer, were not significantly more likely to be in either *Protective Factors* or *Demographic*

and Health System Risks Factors as opposed to *Medical Risk Factors*, when controlling for tumor characteristics.

Chapter 3 is being prepared in part for publication. This publication will be co-authored Vanessa L. Malcarne, Kristen J. Wells, Georgia Robins Sadler, Scott C. Roesch, and Carrie R. McDonald. The dissertation author was the primary investigator and author of this material.

CHAPTER 4: DISCUSSION

The primary goal of the present study was to identify distinct subgroups of patients based on multiple demographic, medical, environmental, and health system factors associated with timeliness of breast cancer care among a sample of 198 patients diagnosed with stage I-III breast cancer who received at least one type of treatment for breast cancer (e.g., surgery, chemotherapy, radiation, anti-hormonal therapy). Latent class analysis (LCA) was employed to simultaneously evaluate patient's age at diagnosis, race/ethnicity, annual household income, insurance coverage, medical comorbidities, family history of cancer, and geographic residence, as well as structural/organizational characteristics of patient's health care facility (i.e., breast cancer services available onsite) to develop a typology of breast cancer patients, and to examine the association between the emergent classes and timely initiation of breast cancer treatment. Additionally, the study's third aim was exploratory and sought to investigate whether disease stage and tumor characteristics, specifically hormone receptor status (estrogen receptor [ER], progesterone receptor [PR]) and human epidermal growth factor receptor 2 (HER2) status, were significantly associated with timeliness of breast cancer treatment initiation and statistically predicted class membership.

Based on statistical evaluation and practical interpretation, a three-class solution was deemed most appropriate. Three latent classes of breast cancer patients emerged with varying patterns of patient demographic, medical, and health system characteristics. The first class comprised approximately 74% of the study sample and was distinguished by its high endorsement of indicators associated with timely breast cancer care and was thus labeled "*Protective Factors*." Patients in this class were more likely to be White and have a family history of cancer than the other two classes. Members of the *Protective Factors* class were

also likely to have private health insurance and to receive care at a health care facility with a greater number of breast cancer-related services available onsite, similar to the third class, and have few comorbid medical conditions, similar to the second class. Across all classes, patients were more likely to have an annual household income of less than $40,000. However, the *Protective Factors* class had a greater proportion of patients who had an income of $40,000 or greater than the other classes (35.4% [Class 1] vs. 0% [Class 2] vs. 14.2% [Class 3]). The second class, accounting for approximately 21% of the sample, was characterized by a greater endorsement of multiple individual and contextual factors associated with treatment delays and was labeled "*Demographic and Health System Risks Factors*." Specifically, breast cancer patients in this class were more likely to have public health insurance, no family history of cancer, and the least amount of breast cancer-related services available onsite at their health care facility than the other classes. Within this class, a greater proportion of members were Hispanic compared to the other race/ethnicities included in the study, African American or White. Lastly, the third class comprised approximately 5% of the sample and was labeled "*Medical Risk Factors.*" This class represented breast cancer patients with the oldest average age at diagnosis and the greatest number of medical comorbidities. Similar to the *Protective Factors* class, patients in this class received care at health care facilities with a greater number of breast cancer-related services available onsite. The *Medical Risk Factors* class was equally as likely to be Hispanic or White and have public health insurance or private health insurance.

The present study's second aim was to examine the association between class membership and timeliness of breast cancer treatment initiation. Results demonstrated that the emergent classes did not significantly differ in the likelihood of initiating any type of breast cancer treatment within 30 days or 60 days from diagnosis, controlling for first type of

treatment received. Specifically, there were no significant differences between patients in the *Protective Factors* and *Demographic and Health System Risk Factors* classes, as compared to patients in the *Medical Risk Factors* class, for initiating chemotherapy compared to surgery, or other treatment compared to surgery, within 30 or 60 days from diagnosis. When evaluating the average number of days to initiate breast cancer treatment from diagnosis (time-to-treatment), the observed means were higher in the *Demographic and Health System Risk Factors* class compared to both the *Protective Factors* class and the *Medical Risk Factors* class, but these differences were not statistically significant. While there were no significant differences across all three classes in the average time-to-treatment for initiating chemotherapy versus surgery as the first treatment, breast cancer patients in the *Protective Factors* class and the *Demographic and Health System Risk Factors* class initiated surgery more quickly than other treatments (i.e., radiation therapy, hormone therapy).

The overall sample size of the present study, as well as small class sizes of *Demographic and Health System Risk Factors* and *Medical Risk Factors* may have obscured statistically significant differences between the emergent classes and the treatment outcomes. A notable problem with small samples is that there may be many categories that are sparse (e.g., cells have zero or small counts). As the possible response patterns increase exponentially with the number of indicator variables, unless the sample size is extremely large, the response frequencies in the contingency table will contain large numbers of empty cells. While there is no definite rule for the minimum sample size needed for LCA, a minimum sample size of $N = 500$ has been suggested based on prior simulation studies (Finch & Bronk, 2011), although it has been acknowledged that such a large samples size may not always be feasible and others have recommended a minimum of 100 (Wurpts & Geiser, 2014). In certain

circumstances a smaller sample size may be acceptable, specifically, when there is a high degree of separation between classes and the observed indicator variables are sensitive to class differences and have responses with large variability (Samuelsen & Raczynski, 2013). Wurpts and Geiser (2014) reported that using more and high quality indicators (highly distinctive and strongly related to the latent class variable) or adding a covariate that is strongly related to class membership may compensate and alleviate some of the frequent problems associated with small sample size, but study samples below $N = 70$ are not feasible under virtually any circumstances due to problems with non-convergence or poor class assignment accuracy. They also recommended that when uncertain about the minimum feasible sample size, researchers conduct their own application-oriented simulation study (Muthén & Muthén, 2002), or pilot studies to identify the best latent class indicators and covariates. The indicators used by the present study were selected based on previous research that demonstrated significant associations between each of those variables and timeliness of breast cancer care. As such, eight indicators were chosen to reflect a constellation of demographic, medical, environmental, and health system characteristics associated with timely breast cancer care. While it was hypothesized that these indicators would be strongly related to the latent class variable, it was unknown which indicator or combination of indicators would be highly distinctive and characteristic of the latent classes, and whether other indicators of individual and contextual factors would be more meaningful and significantly related to timeliness of treatment initiation.

Although the present study did not find that the emergent classes were significantly associated with timeliness of breast cancer treatment initiation, the specific constellations of characteristics that distinguish the classes provide initial support for using LCA as an alternate

approach for evaluating how multiple individual and contextual factors cluster together to define groups and warrant further investigation. The *Demographic and Health System Risk Factors* class represents a subgroup of patients with more limited resources and access to high-quality breast cancer care. Women with lower SES generally experience greater cancer burden and significant barriers to care compared to those with higher SES (American Cancer Society, 2018). Limited health insurance coverage negatively impacts one's ability to access health care services, and racial/ethnic minorities are more likely to be uninsured and to have lower income than non-Hispanic whites (Ward et al., 2008). Studies have demonstrated that low income and public health insurance (e.g., Medicaid, Medicare) or lack of insurance are significant predictors of treatment delays for initiating surgery (Gwyn et al., 2004; Smith, E. C. et al., 2013) and adjuvant breast cancer treatments (Chavez-MacGregor et al., 2016; Fedewa et al., 2010; Freedman et al., 2013; Wheeler et al., 2012a). However, in addition to these socioeconomic risk factors, breast cancer patients in the *Demographic and Health System Risk Factors* class notably were most likely to receive care at health care facilities that provided the least amount of breast cancer services onsite compared to the other latent classes. Decentralization and fragmentation of care may create additional barriers to accessing timely, high-quality cancer care. As studies have shown mixed results regarding structural/organizational characteristics of health care systems impacting timeliness of breast cancer treatment initiation, future studies should evaluate how other health system factors, such as distance to facility, facility size/volume, and type of facility, are interrelated with patient sociodemographic and medical characteristics. For example, Wheeler et al. (2012b) reported attending a health care facility that was for-profit/private (OR = 1.35; $p < .01$), had on-site radiation services (OR = 1.35; $p < .01$), and was smaller and had fewer beds (OR =

1.08; $p < .05$) were signifiantly associated with higher odds of initiation of radiation therapy within two months of diagnosis, while another study found surgicial facility type/ownership, distance traveled to facility, and facility size were not predictive of initiating adjuvant chemotherapy within four months of diagnosis (Wheeler et al., 2012a). Health system factors may have differential effects as they are related to specific constellations of other idividual and contextual characteristics.

The classes demonstrated differences in family history of cancer, aging, and comorbid health conditions. Although the effect of family history of cancer on timeliness of breast cancer treatment initiation is not yet well-established, it has been hypothesized that a family history of cancer would be associated with shorter treatment delays as health care system may respond more rapidly to women with a higher risk of cancer, who were more likely to be in Class 1 (*Protective Factors*). Despite the small class size, the *Medical Risk Factors* represents a distinct class of breast cancer patients who are older and have multiple medical conditions. As the number of comorbid medical conditions significantly increase with age, such that 80- to 89-year old patients have an average of five serious comorbidities versus 50- to 59-year old patients have an average of one or two serious comorbidities (Yancik et al., 2001), older breast cancer patients may experience unique barriers to care and breast cancer treatment delays due to their comorbid medical conditions and other factors associated with older age, including worse general health, reduced mobility, and lower functional status. Treatment decisions may also be further complicated and delayed due to the lack of established breast cancer treatment guidelines for older patients with and without comorbidities. Contrary to previous research, the *Medical Risk Factors* class did not experience significant delays in treatment initiation compared to the other two classes. Of note, the average age of diagnosis

for this class was 66.56 years, which is relatively close to the population median age of 62 years at diagnosis in the United States (American Cancer Society, 2017) and is lower compared to studies that have found significant associations between increasing age, specifically 70 years or older, and treatment delays (Fedewa et al., 2010; Freedman et al., 2013; Hershman et al., 2006a, 2006b). Additionally, compared to the *Demographic and Health System Risk Factors* class, breast cancer patients in the *Medical Risk Factors* class received care at a health care facility that provided a greater number of breast cancer related services onsite, which may serve as a protective factor for timely treatment initiation and be associated with health insurance coverage.

Finally, the last aim of the study was to explore how stage of breast cancer and tumor characteristics (ER status, PR status, and HER2 status) were related to timeliness of breast cancer treatment initiation and to the emergent latent classes. Results demonstrated no significant differences in the likelihood of initiating some type of breast cancer treatment within 30 days or 60 days from diagnosis between patients whose breast cancer was diagnosed as stage I or stage II, as compared to patients whose breast cancer was diagnosed as stage III. Of note, the average time-to-treatment from diagnosis was significantly shorter for patients with stage I and stage II breast cancers compared to the patients with stage III breast cancers, potentially reflecting the fact that treatment planning in patients with cancer diagnosed at later stages may be more complex. In regards to class membership, no statistically significant differences were found among the emergent classes with regard to cancer stage or tumor characteristics.

While a growing number of studies have identified a number of factors associated with delays in breast cancer care, studies have varied in their definitions of treatment delays and

have used multiple time intervals with different starting points, such as evaluating timely initiation of any treatment or a specific type of treatment for breast cancer (e.g., surgery, adjuvant treatments) following definitive diagnosis or from surgery to an adjuvant treatment (e.g., adjuvant chemotherapy). These methodological differences may contribute to mixed study results. Prior research has also been limited by the lack of established guidelines for standard of care regarding timely initiation of breast cancer treatment. As an intermediate outcome, delays in breast cancer care only matter if they are associated with other outcomes impacting patient morbidity and mortality, such as increased need for more invasive treatment, increased treatment-related complications, decreased quality of life, or decreased survival. A recent systematic review indicated that diagnosis and initiation of treatment for breast cancer within 90 days increases survival (Williams, F., 2015), and a recent meta-analysis of survival and time to initiate adjuvant chemotherapy demonstrated that a delay of 30 days or more after surgery is associated with worse overall and disease free survival (Zhan, Fu, Fu, Zhang, & Wang, 2018). The present study evaluated timely initiation of any breast cancer treatment within 30 or 60 days from diagnosis. Across all study participants, the average time to initiate any breast cancer treatment from diagnosis was 47.99 days (*SD* = 43.98), and all three classes initiated treatment within 60 days. Overall, a limited number of study participants experienced significant delays in treatment initiation, which may have contributed to the study results demonstrating a lack of significant association between class membership and timeliness of breast cancer treatment initiation. Breast cancer patients in *Protective Factors* and *Demographic and Health System Risk Factors* classes initiated surgery more quickly compared to other treatment, such as hormone or radiation therapy.

The results from the present study must be interpreted within the context of several limitations to the study. First, the overall study sample size was relatively small for a LCA with eight indicator variables, and the small sample sizes of the two greater risk factor classes may have affected precision of estimated associations between the classes and treatment outcomes. Larger studies with more diverse patient characteristics are needed to confirm identification of distinct subgroups of breast cancer patients and to investigate the predictive utility of emergent classes on timeliness of breast cancer treatment initiation. Second, the present study utilized archival data from the PNRP, specifically the control arm, and was thus limited in the available indicator variables for examination and study sites did not record all the same variables across sites for the control participants, further limiting the study sample size. The present study only used one indicator for patient's environment (i.e., whether the patient resided in an urban or rural geographic residence) and one indicator for health system (i.e., number of breast cancer related services available onsite) factors. However, there was no variability in the patient geographic residence variable, as all but one patient in this study resided in an urban residence, and its effect was unable to be ascertained. Additional contextual factors of patient's environment and health care system should be evaluated, such as neighborhood-level SES, racial/ethnic composition of neighborhoods, distance to health care facility, type of facility, and facility size/volume. For example, Kim and authors (2015) utilized LCA to identify distinct classes of neighborhoods, and found that African American women living in racially heterogeneous middle class neighborhoods had a longer time to follow-up after an abnormal mammogram compared with African American women living in predominantly black middle class neighborhoods. Other important patient demographic factors that should be considered in future studies include patient's education level and

martial status. Third, due to sample size limitations, Asian, Native Hawaiian/Pacific Islander, and American Indian/Alaska Native breast cancer patients were unable to be examined or included as a race/ethnicity variable, and the proportion of African American women in the study sample was relatively small. A larger, more ethnically diverse sample of breast cancer patients is needed to fully explore the role of race/ethnicity in combination with the other individual and contextual factors. Fourth, the present study did not include clinical characteristics of the cancer (i.e., disease stage and hormone receptor status) in the formulation of latent classes due to uncertainty of when the information was recorded (e.g., before or after treatment initiation). The included latent class indicators were selected based on prior research demonstrating significant association with timeliness of breast cancer care, and that these observed variables were measured prior to treatment initiation in order to assess whether the latent classes predicted timely initiation of breast cancer treatment. However, as the stage and type of breast cancer (e.g., ER+/ER-, PR+/PR-, HER2+/HER2-) have important prognostic value and implications for type of treatment received, clinical and tumor characteristics should be included in future studies and simultaneously evaluated with other patient demographic, medical, environmental, and health system factors. A recent study demonstrated that patients with stage IV breast cancers had shorter median time-to-treatment (27.5 days) compared to patients diagnosed with earlier breast cancer stages (35, 37, and 37 days for stage I, II, and III respectively) (Khanna et al., 2017); however, the approach to optimal treatment planning and timing of treatment for metastatic disease substantially differs from an earlier stage cancer, and often varies according to individual differences, including hormonal status, patient symptoms, previous treatments, and treatment preferences. Further research is needed to understand individual and contextual differences between patients

diagnosed with stage I, II, and III breast cancers and its associations with tumor characteristics (e.g., hormonal receptor status, tumor size, tumor grade) and specific type of treatment. Lastly, the generalizability of the results is limited by the characteristics of the study sample. Specifically, all participants in the present study had stage I-III breast cancer and lived in urban areas, and a majority of participants were White, had lower income, and received surgery as their initial breast cancer treatment. Thus, results do not generalize to breast cancer patients with metastatic cancer (stage IV), with higher socioeconomic status, or living in rural areas.

This study was the first to use a person-centered approach to model multiple demographic, medical, environmental, and health system factors in terms of timeliness of breast treatment initiation. While three classes of breast cancer patients were identified with unique patterns of individual and contextual characteristics, the emergent classes did not significantly differ in terms of timely initiation of breast cancer treatment following definitive diagnosis of cancer. Although the present study was unable to establish a typology of breast cancer patients for timely initiation of breast cancer treatment, further investigation is warranted to confirm the existence of distinct subgroups with varying demographic, medical, environmental, and health system characteristics among a larger, more diverse sample of breast cancer patients. Including additional indicators representing multiple dimensions of individual and contextual risks for treatment delays may improve identification of substantively meaningful and distinct classes of breast cancer patients, particularly those with greater risks of experiencing delays in breast cancer care, which could help inform interventions and direct efforts to those recipients that would benefit the most from additional

services and allow for a more targeted and effective approach to improving breast cancer outcomes.

Chapter 4 is being prepared in part for publication. This publication will be co-authored Vanessa L. Malcarne, Kristen J. Wells, Georgia Robins Sadler, Scott C. Roesch, and Carrie R. McDonald. The dissertation author was the primary investigator and author of this material.

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Table 1. Sample Characteristics

Variable	*n*	Percent
Demographics		
Age (years)[a]	56.56 (11.35) Range: 24-82	
Race/ethnicity		
White	102	51.5%
Hispanic/Latino	50	25.3%
Black/African American	37	18.7%
Asian	1	0.5%
Native Hawaiian/Pacific Islander	1	0.5%
Missing	7	3.5%
Annual household income		
< $40,000	94	47.5%
≥ $40,000	41	20.7%
Missing	63	31.8%
Health insurance		
Private	83	14.6%
Public	85	42.9%
Uninsured	29	41.9%
Missing	1	0.5%
Medical History		
Medical comorbidities[a,b]	0.43 (0.97)	
Family history of cancer		
Yes	110	55.6%
No	85	42.9%
Missing	3	1.5%
Environmental/Geographic residence		
Urban	195	98.5%
Rural	1	0.5%
Missing	2	1%
Health System		
Breast cancer services on-site[a]	4.25 (2.28)	

Table 1: Continued

Variable	*n*	Percent
Stage of Breast Cancer		
Stage I	71	35.9%
Stage II	70	35.4%
Stage III	37	18.7%
Missing	20	10.1%
Tumor Characteristics		
ER Status		
ER-	48	24.2%
ER+	131	66.2%
Missing	19	9.6%
PR Status		
PR-	65	32.8%
PR+	112	56.6%
Missing	21	10.6%
HER2 Status		
HER2-	144	72.7%
HER2+	27	13.6%
Missing	27	13.6%
Breast Cancer Treatment		
Chemotherapy	26	13.1%
Lumpectomy	81	40.9%
Mastectomy	69	34.8%
Other	5	2.5%
Missing	17	8.6%

Note: [a]*Mean* (*Standard Deviation*); ER-: estrogen receptor negative; ER+: estrogen receptor positive; PR-: progesterone receptor negative; PR-: progesterone receptor positive; HER2-: human epidermal growth factor receptor 2 protein negative; HER2+: human epidermal growth factor receptor 2 protein positive.

Table 2. Model Fit Indices

No. of classes	Log Likelihood	AIC	sBIC	LMRT *p*-value	BLRT *p*-value	Entropy
1	-2083.98	4193.96	4195.52	---	---	---
2	-2000.82	4049.64	4052.53	< .001	< .001	0.796
3	-1848.396	3766.793	3771.002	.0121	< .001	0.995
4	-1786.597	3665.193	3670.725	.0006	< .001	0.926
5	-1769.524	3653.048	3659.903	.1026	< .0001	0.889

Note. AIC: Akaike Information Criteria; sBIC: sample size-adjusted Bayesian Information Criterion; LMRT: Lo-Mendell-Rubin Adjusted Likelihood Ratio Test; BLRT: Bootstrapped sLikelihood Ratio Test

Table 3. Class-Specific Item Response Means and Probabilities From the Three-Class Latent Class Analysis

	Latent Classes		
	Class 1 (n = 147)	Class 2 (n = 42)	Class 3 (n = 9)
Demographic Factors			
Age[a]	56.578 (0.878)	54.243 (2.007)	66.557 (3.985)
Race/ethnicity			
African American	0.183	0.263	0.110
Hispanic	0.198	0.472	0.441
White	0.619	0.265	0.449
Annual household income			
< $40,000	0.646	1.000	0.858
≥ $40,000	0.354	0.000	0.142
Health insurance			
No insurance	0.143	0.171	0.111
Public insurance	0.367	0.659	0.444
Private insurance	0.490	0.170	0.444
Medical Factors			
Medical comorbidities[a]	0.258 (0.041)	0.379 (0.125)	3.985 (0.344)
Family history of cancer			
No	0.373	0.657	0.442
Yes	0.627	0.343	0.558
Environmental Factors			
Patient Geographic Residence			
Rural	0.007	0.000	0.000
Urban	0.993	1.000	1.000
Health System Factors			
Breast cancer services onsite[a]	5.392 (0.061)	0.078 (0.055)	5.334 (0.156)

Note. [a]Mean (Standard Error)

Table 4. Odds Ratios for the Effect of Class Membership on Timeliness of Breast Cancer Treatment Initiation Within 30 Days or 60 Days

	Class 1[a]		Class 2[a]	
	OR	95% CI	OR	95% CI
Within 30 days				
Any treatment	0.962	-0.232 to 2.156	0.694	-0.338 to 1.727
Chemotherapy[b]	0.407	0.154 to 1.070	3.600	0.633 to 20.476
Other[b]	0.001	0.001 to 0.001	0.001	0.001 to 0.001
Within 60 days				
Any treatment	0.560	-0.447 to 1.567	0.464	-0.462 to 1.390
Chemotherapy[b]	0.637	0.265 to 1.534	1.231	0.156 to 9.712
Other[b]	0.001	0.001 to 0.001	0.001	0.001 to 0.001

Note. [a]Class 3 was the reference class; [b]Surgery was the reference treatment group; OR: odds ratio; 95% CI: 95% confidence interval range.

Table 5. Mean Differences in Timeliness of Breast Cancer Treatment Initiation By Class Membership

	Class 1	Class 2	Class 3
Time to Initiate Breast Cancer Treatment	β^a (*SE*)	β^a (*SE*)	β^a (*SE*)
Intercept	44.900 (3.560)	54.235 (15.838)	39.750 (8.221)
Chemotherapy[b]	14.160 (11.160)	-8.635 (23.465)	16.196 (0.000)
Other[b]	29.149 (3.571)	40.765 (19.884)	7.250 (8.221)
Overall Mean (*SE*)	47.119 (3.460)	56.119 (13.127)	40.556 (7.347)

Note. [a]Regression coefficient; [b]Surgery was the reference treatment group; SE: standard error.

Table 6. Odds Ratios For the Effect of Disease Stage and Tumor Characteristics on Timeliness of Breast Cancer Treatment Initiation

	Treatment Initiation Within 30 Days			Treatment Initiation Within 60 Days		
	β^a (*SE*)	OR	*P*	β^a (*SE*)	OR	*P*
Stage of Breast Cancer						
Stage 1[c]	0.681 (0.505)	1.976	.177	0.489 (0.524)	1.631	.350
Stage 2[c]	0.834 (0.491)	2.303	.089	0.723 (0.533)	2.060	.176
Tumor Characteristics						
ER Status[d]	1.055 (0.669)	2.871	.115	0.963 (0.717)	2.550	.191
PR Status[d]	-0.626 (0.612)	0.535	.306	-0.445 (0.594)	0.641	.454
HER2 Status[d]	-0.762 (0.574)	0.529	.206	-0.280 (0.659)	0.756	.671

Note. [a]Logits; [b]Mean Differences; [c]Reference group = Stage 3; [d]Reference group = Positive Status; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2 protein; SE: standard error; OR: odds ratio.

Table 7. Effect of Disease Stage and Tumor Characteristics on Average Time-to-Treatment Initiation From Diagnosis

	Average Time to Treatment		
	M (*SE*)	M_{diff} (SE_{diff})[a,b]	*P*
Stage of Breast Cancer			
Stage 1	33.448 (7.078)	-24.801 (9.678)	.011
Stage 2	34.030 (6.699)	-24.219 (9.514)	.012
Stage 3[a]	58.249 (7.733)	Ref.	Ref.
Tumor Characteristics			
ER-	29.407 (8.909)	-25.003 (12.756)	.052
ER+[b]	54.411 (7.098)	Ref.	Ref.
PR-	48.724(6.796)	13.629 (11.342)	.231
PR+[b]	35.094 (8.157)	Ref.	Ref.
HER2-	47.640(4.803)	11.463 (10.543)	.279
HER2+[b]	36.178 (8.994)	Ref.	Ref.

Note. [a]Reference group = Stage 3; [b]Reference group = Positive status; Ref: reference group; ER-: estrogen receptor negative; ER+: estrogen receptor positive; PR-: progesterone receptor negative; PR-: progesterone receptor positive; HER2-: human epidermal growth factor receptor 2 protein negative; HER2+: human epidermal growth factor receptor 2 protein positive; M: mean; SE: standard error.

Table 8. Disease Stage and Tumor Characteristics as Predictors of Class Membership

	Class 1[a]			Class 2[a]		
	β^b (*SE*)	OR	*P*	β^b (*SE*)	OR	*P*
Stage of Breast Cancer						
Stage 1[c]	0.121 (0.752)	1.129	.872	-0.053 (0.954)	0.948	.956
Stage 2[c]	0.872 (0.826)	2.392	.291	1.301 (0.978)	3.673	.183
Tumor Characteristics						
ER Status[d]	0.545 (1.107)	1.725	.623	-1.527 (1.615)	0.217	.344
PR Status[d]	0.547 (1.066)	1.728	.608	1.837 (1.585)	6.278	.246
HER2 Status[d]	-0.077 (0.766)	0.926	.920	0.318 (0.887)	1.374	.720

Note. [a]Reference group = Class 3; [b]Logits; [c]Reference group = Stage 3; [d]Reference group = Positive status; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2 protein; SE: standard error; OR: odds ratio.