2011

BREAST CANCER TRENDS AMONG KENTUCKY WOMEN, 2004-2007

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BREAST CANCER TRENDS AMONG KENTUCKY WOMEN, 2004-2007

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THESIS

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A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Sciences
College of Agriculture
at the University of Kentucky

By

Kara Ann Hagan

Lexington, KY

Director: Kwaku Addo, PhD, Associate Professor of Nutrition and Food Science

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2011

ABSTRACT OF THESIS

BREAST CANCER TRENDS AMONG KENTUCKY WOMEN, 2004-2007

The purpose of this study is to investigate the discrepancies of female breast cancer mortality between the Appalachian and Non-Appalachian regions of Kentucky using data from the Kentucky Cancer Registry. This study identified subtype, reproductive, and regional differences in women with breast cancer in Kentucky. Among women with breast cancer living in Kentucky from 2004 to 2007, one and three live births significantly increased a woman's risk of breast cancer mortality by 91% and 58% respectively, compared to a woman with zero live births. Progesterone receptor-negative tumor status significantly increased a woman's risk of breast cancer mortality by 64% compared to women with progesterone receptor-positive breast cancer. Residence in the Appalachian region significantly increased a woman's risk of breast cancer mortality by 3.14-fold. After adjusting for regional interactions, progesterone receptor-negative tumor status in the Appalachian region increased a woman's risk of breast cancer mortality by 3.13-fold. These findings suggest parity and estrogen receptor tumor status do not contribute to the breast cancer differences between the Appalachian and Non-Appalachian region of Kentucky. The association between progesterone receptor status and Appalachian residency suggest factors associated with the Appalachian region provide the poorest prognosis for a woman with breast cancer in Kentucky.

KEYWORDS: Breast cancer, Mortality, Appalachia, Parity, Progesterone

Kara Ann Hagan

December 8, 2011

BREAST CANCER TRENDS AMONG KENTUCKY WOMEN, 2004-2007

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December 8, 2011
Date

DEDICATIONS

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In memory of my grandfather

Robert Michael Hagan

1947 – 2000

&

My lovely grandmother and three-time breast cancer survivor

Lois Ann Hagan

ACKNOWLEDGEMENTS

The successful completion of the following thesis would have not been feasible without the support and direction of many key people. First and foremost I want to thank my Thesis Chair, Dr. Kelly Webber. I am sincerely grateful for the guidance and motivation throughout my academic career and in the preparation of my thesis. I am also thankful for the example she has provided as a successful woman researcher and professor. Next, I want to thank Dr. Alison Gustafson, whose significant contributions and invaluable guidance allowed me to see this project to completion, as well as, Dr. Kwaku Addo, for his words of encouragement and participation on my thesis committee.

In addition to my thesis committee members, I have been blessed to have three important mentors that have been monumental in my academic career at the University of Kentucky. Dr. Sandra Bastin, you are an inspiration. Thank you for inspiring me to be a leader to others and to never give up on my dreams. Dr. Tammy Stephenson, without you, I don't think I would have made it through graduate school. Thank you for always being in my corner. And, Dr. Bernhard Hennig, because of you, I was able to realize my full potential as a student and teacher to others.

I also wish to thank the Kentucky Cancer Registry for providing the breast cancer data and the KCR staff for their time and advice on this project. I also must thank all of the NFS faculty and staff for their support during my academic career.

Finally, my deepest gratitude goes to my parents, family, friends and fellow graduate students for their love and support. I hope that I continue to make you proud. And last but not least, Michael, whose patient love enabled me to complete this project. My success is nothing without you.

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CHAPTER ONE

Introduction

Background

Breast cancer is the most commonly occurring cancer among women in Kentucky (Centers for Disease Control and Prevention [CDC], 2010). Research has associated unfavorable socioeconomic and reproductive factors with an increased risk of female breast cancer and incidence of specific tumor markers (L. Vona-Davis et al., 2008). Non-Appalachian regions have higher incidence rates, whereas Appalachian women experience higher breast cancer mortality rates (Appalachian Regional Commission [ARC], 2004). These Appalachian regions of Kentucky are known to have decreased access to health care, lower personal incomes, and lower rates of breast cancer screening (Hall, Uhler, Coughlin, & Miller, 2002; McGarvey, Killos, & Cohn, 2011; Wingo et al., 2008). Other factors unique to the Appalachian region may be significant predictors of breast cancer incidence and mortality (Katz et al., 2010; McGarvey, et al., 2011). Therefore, studying how these risk factors predict the vital status of Kentucky women with breast cancer can aid health professionals in developing educational and preventative techniques to decrease incidence and mortality in both Appalachian and Non-Appalachian regions of Kentucky.

Statement of the Purpose

The purpose of this study is to investigate the breast cancer mortality rate differences among women living in the Appalachian and Non-Appalachian regions of Kentucky. By investigating the subtype, lifestyle, and reproductive differences between

the two regions of Kentucky, investigators and health care professionals can focus their education efforts, screening procedures, and prevention efforts to the needs of each region

Research Questions

1. Does the number of live births have an effect on the breast cancer mortality variation among adult women with breast cancer living in Kentucky?

2. Does the tumor receptor status have an effect on mortality in women with breast cancer living in Kentucky?

3. What factors contribute to the mortality difference between the Appalachian and Non-Appalachian region in women with breast cancer living in Kentucky?

Justification

Kentucky is the only state out of the six main Appalachian states, which includes Ohio, Pennsylvania, Virginia, New York, and West Virginia, whose breast cancer mortality rate is greater in the Appalachian region than the Non-Appalachian region of the state (Appalachian Community Cancer Network [ACCN], 2010; ARC, 2009). Research efforts have established socioeconomic, lifestyle, and reproductive factors to be associated with mortality and incidence rates in other Appalachian states (Abraham et al., 2009; Katz, et al., 2010; McGarvey, et al., 2011). However, limited research is available defining the regional differences of breast cancer mortality between the Appalachian and Non-Appalachian region of Kentucky (Burris & Andrykowski, 2010; Wingo, et al., 2008). Thus, research efforts are warranted to explain the relationship of risk factors with

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breast cancer mortality in both the Appalachian and Non-Appalachian regions of Kentucky in order to help decrease overall breast cancer mortality rates in Kentucky.

Assumptions

This study assumed all data collected by the Kentucky Cancer Registry was accurate. Secondly, the study also assumes records that were excluded did not skew the results. Lastly, the study concludes breast cancer mortality in the current cases and future cases would be related to the diagnosis of breast cancer.

CHAPTER TWO

Literature Review

Breast cancer mortality rates in Appalachia Kentucky are significantly higher than rates in Non-Appalachian regions of the state (Wingo, et al., 2008). Though smoking, family history, and personal history are established risk factors of female breast cancer incidence, mortality rate discrepancies of breast cancer between Appalachian and Non-Appalachian regions may be linked to reproductive, subtype, or socioeconomic regional differences (Luo et al., 2011; McDavid, Tucker, Sloggett, & Coleman, 2003; Phipps et al., 2011; L Vona-Davis & Royce, 2009). The study of these regional differences may provide insights into understanding and minimizing the risk factors associated with aggressive breast cancer subtypes.

Pathology of Cancer

The pathology of cancer is an important focus in the research of breast cancer. Understanding the pathology of breast cancer is essential in the prevention and reduction of breast cancer, as well as treatment efforts for breast cancer (Lari & Kuerer, 2011; Ursin et al., 2005).

Current research hypothesizes that mutations in tumor suppressing genes, imbalances of regulating proteins, and over expressions of tumor receptors are involved in the proliferation mechanism (Lari et al, 2011). Breast cancer research links increased endogenous estrogen and progesterone levels with decreased cell adhesion and increased trans-epithelial permeability. Decreased levels of trans-epithelial resistance may allow cancer-causing agents to diffuse easily through the tissue (Bernstein & Lacey, 2011;

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Martin, Das, Mansel, & Jiang, 2007). Cancer cells may fail to promote the expression of unique receptors on the cell to signal the immune system to execute apoptosis via cytotoxic T cells (Martin, et al., 2007; L. Vona-Davis & Rose, 2009). The cancer cells are able to proliferate without mediation from the immune system resulting in metastasis (Jerry, Dunphy, & Hagen, 2010; Martin, et al., 2007).

However, research is still inconclusive over the exact pathology of breast cancer pathology. We now know it is not one gene, one risk factor, or one event that causes breast cancer (Bernstein & Lacey, 2011; Milne et al., 2010; Phipps, et al., 2011). Instead, we can conclude that there are numerous genes, factors, and events that contribute to the pathology of breast cancer.

Tumor Receptors

Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor (HER2) are three tumor markers used to diagnose, determine treatment, and classify subtypes of breast cancer (Albrektsen, Heuch, & Thoresen, 2010). Researchers have used these tumor markers to investigate the risk factors of breast cancer subtypes and the aggressiveness of each subtype (Bernstein & Lacey, 2011). Estrogen receptor-positive and progesterone receptor-positive tumor markers have been characterized to have more favorable responses to hormonal therapy and better prognoses (Bernstein & Lacey, 2011; Jerry, et al., 2010). Research proposes reproductive, socioeconomic, and lifestyle influences to predict specific tumor receptor markers in females with breast cancer (Bernstein & Lacey, 2011; Burris & Andrykowski, 2010; McGarvey, et al., 2011). Various subtypes have been associated with different rates of mortality, pathology, and response to standardized treatment methods Over expressions of tumor receptors have

been correlated with tumor cell proliferation in conjunction with mutations in tumor suppressing genes and imbalances in regulating proteins (Jerry, et al., 2010; Lari & Kuerer, 2011; Perks & Holly, 2011). A subtype of breast cancer, characterized as estrogen receptor-negative/progesterone receptor-negative/human epidermal growth factor receptor 2 negative subtype, also known as "triple-negative," may have risk factors that are hormonally or non-hormonally stimulated (Phipps, et al., 2011; Rakha et al., 2009). In 2011, Phipps et. al. found nulliparity to be associated with an increased risk of estrogen receptor-positive breast cancer, but it was not associated with the risk of estrogen receptor-negative or triple-negative breast cancer (2011). Various researchers have associated this aggressive, unconventional subtype of breast cancer with poor socioeconomic factors in rural populations (Abraham, et al., 2009; L. Vona-Davis, et al., 2008). Additional research has also associated obesity, race, young age, and a possible genetic anomaly with this triple-negative breast cancer subtype (McGarvey, et al., 2011; Linda Vona-Davis & Rose, 2009). However, research investigating these tumor receptor markers related to the vital status of adverse socioeconomic regions, specifically the Appalachian region of Kentucky, is novel and limited.

Reproductive Factors

Research concludes parity, early age of first pregnancy, and premenopausal status are negatively associated with breast cancer risk in women (Albrektsen, et al., 2010; Huiyan et al., 2010; Milne, et al., 2010). Research has found high parity to be negatively associated with breast cancer mortality in adult women (Phipps, et al., 2011). One study observed a 50% decrease in breast cancer incidence, with a full term pregnancy early in reproductive life (Jerry, et al., 2010). Research studies have attributed this decreased

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risk of breast cancer development to the decreased oscillation of these hormones during pregnancy versus the nulliparous state (Jerry, et al., 2010; Ursin, et al., 2005). Obesity in premenopausal women has been correlated with a protective effect against the development of breast cancer, specifically affecting the levels of endogenous circulation of ovarian hormones (Conroy et al., 2011; Smigal et al., 2006). Premenopausal breast cancer has been associated with more aggressive tumor subtypes, larger tumor sizes, increased lymphatic involvement, and increased recurrence. On the other hand, postmenopausal status has been associated with less aggressive hormone-stimulated tumor receptor markers in females with breast cancer (Conroy et al., 2011; Smigal, et al., 2006; Vona-Davis & Rose, 2009). Yet, postmenopausal obesity has been linked to an increased risk of breast cancer incidence and decreased vital status. Increased postmenopausal adipose tissue is thought to stimulate an overproduction of endogenous hormones that promotes the formation of abnormal breast cells (Conroy, et al., 2011; Smigal, et al., 2006; Vona-Davis & Rose, 2009). Available epidemiological and hospital record data for Kentucky limits the ability of researchers to correlate obesity to hormone stimulated tumor receptor status and mortality rate in both the Appalachian and Non-Appalachian region. Therefore, future development of data collection methods including dietary and anthropometric fields could better promote the development of a better breast cancer mortality rate prediction model.

Regional Differences

The Appalachian region represents 52 of the 120 counties in the state of Kentucky (Kentucky Cancer Registry, 2011). This region has been historically categorized as medically underserved with poor socioeconomic conditions (Hall, et al., 2002).   Current

literature suggests a need for more research to investigate how socioeconomic factors influence the mortality rate of women with breast cancer. Researchers hypothesize that various socioeconomic factors, in addition to tobacco use, reproductive factors, and genetics have an impact on breast cancer vital status (Huang, Dignan, Han, & Johnson, 2009; Land et al., 2011; L Vona-Davis & Royce, 2009). Poor socioeconomic factors, including low education rates, low average annual salary, and decreased access to health care have been correlated to high rates of breast cancer incidence (Burris & Andrykowski, 2010; McDavid, et al., 2003; Royse & Dignan, 2009).

According to the Appalachian Regional Commission (2009), the average annual salary of the Appalachian region of Kentucky is $28,979. The socioeconomic status of this region is of concern since this average salary is more than $5000 less than the national and state averages and $4,818 less than the remaining United States Appalachian region. Consequently, this region has the highest poverty rate and lowest high school graduation rate in all Appalachia (ARC, 2009).

Previous research focusing on cancer knowledge and screening intentions concluded access to health care to be an important predictor of cancer vital status in the Appalachian region of Kentucky (McDavid, et al., 2003; Royse & Dignan, 2009). In 2009, Royce and Dignan associated decreased health insurance coverage and screening education with low levels of screening procedures. The study discovered over 25% of the study participants did not know there was a test for breast cancer and over half were unable to identify at least one warning sign of cancer. The population with the lowest education level was most likely to be among the 56.5% of participants that were unable to identify any of these warning signs (Royse & Dignan, 2009). The findings provide

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evidence to suggest the Appalachian region of Kentucky is less educated about preventative measures and the symptoms of breast cancer (Huang, et al., 2009; Royse & Dignan, 2009).

Research investigating populations in the Appalachian counties of Virginia also found socioeconomic factors, such as low income, lack of education, and decreased access to medical care, to contribute to adverse health disparities in Appalachian regions (McGarvey, et al., 2011). However, this study failed to significantly correlate health insurance coverage to health care utilization.

Research concludes populations in Appalachia are less likely to seek medical care due the inconvenient travel associated with seeking specialized care and the lack of income and insurance coverage to pay medical fees (Burris & Andrykowski, 2010; Huang, et al., 2009; McDavid, et al., 2003). As a result, individuals are procrastinating medically necessary screening procedures and delaying preventative care (Royse & Dignan, 2009). More research involving socioeconomic factors is imperative to generate a more accurate prediction model for breast cancer vital status.

Tumor Classifications by Stage and Grade

Tumor classifications by stage and grade, are used by medical professionals and researchers to classify the physical characteristics of cancer cells (Young, Roffers, Reis, Fritz, & Hurlburt, 2001). Poor socioeconomic factors are linked to less optimal breast cancer classifications (L Vona-Davis & Royce, 2009). Prolonged diagnosis is associated with a more aggressive breast cancer progression, more invasive cancer, and negative vital status (Huang, et al., 2009). The delayed utilization of health care and screening

procedures may accompany a later stage and higher tumor grade of breast cancer at diagnosis (Hall, et al., 2002).

The National Cancer Institute's Surveillance Epidemiology and End Results classification system is used to classify the progression stage of breast cancer. According to the 2000 SEER Summary Staging Manual, Stage I is defined as a localized cancer. *"A localized cancer is a malignancy limited to the organ of origin"* (Young, et al., 2001). The cancerous cells are in the fat and breast tissue, which includes the nipple and/or areola, and have not metastasized to other organs of the body. A cancer is upgraded to Stage II when it is no longer confined to the breast tissue. Specifically, the cancer has infiltrated a surrounding tissue or muscle. The cancer is defined as Stage III when the cancer has spread into the lymphatic system. When the cancer has metastasized in other organs of the body via tissue and lymphatic system, the breast cancer is categorized as Stage IV. A less known classification, Stage VII breast cancer is defined as a distant metastasis with lymphatic involvement. For example, a woman is classified as having Stage IV if her primary location of cancer is in the breast with a satellite metastasis in the adrenal gland (Young, et al., 2001). However, it is important to understand there are limitations to the staging system. Research involving the incorporation of breast cancer staging may have an increased margin of error depending on the variability of physician differentiation characteristics and on the ability to accurate classify to cancer associated with degree of metastatic clarity (Young, et al., 2001).

According to Young et al., (2001), the National Cancer Institute defines tumor grade as *"a system used to classify cancer cells in terms of how abnormal they look under a microscope and how quickly the tumor is likely to grow and spread."* The scale is 1 – 4,

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with 1 being well differentiated to 4 being undifferentiated or anaplastic. Grade 4 tumors are considered the most aggressive grade (Young, et al., 2001). Research investigating breast cancer history related to reproductive factors in a Norwegian population provided evidence to support previous research works associating prolonged diagnosis, later age at diagnosis, and nulliparity to be associated with a higher histological grade of breast cancer tumors (Albrektsen, et al., 2010). Poorly differentiated tumors were most associated with younger age, with the most significance in nulliparious women. This study emphasized a large gap in breast cancer research. Current research fails to unify the associations of tumor classifications, reproductive factors, and socioeconomic influences to breast cancer vital status.

Future researchers should analyze these risk predictors with tumor receptors to investigate if poorly differentiated tumors in young, nulliparious women are associated with triple-negative breast cancer. In addition, socioeconomic factors related to tumor classifications controlling for reproductive and lifestyle factors would construct a more valid prediction model for breast cancer vital status.

CHAPTER THREE

Methodology

Research Methods

This research study was approved by the Institutional Review Board (IRB) at the University of Kentucky, in April 2011. Once the study was approved, applications were submitted to the Kentucky Cancer Registry to obtain research data fields. Permission to use the data was granted by the Kentucky Cancer Registry review panel in May 2011. The Kentucky Cancer Registry informatics staff created a de-identified data file that was transferred over the Kentucky Cancer Registry secure transfer site. The data was accessed using an assigned username and password. The data included individual, record-level data with no personal identifiers.

This study used a cross-sectional observational epidemiologic framework. The data supplied by the Kentucky Cancer Registry provided demographic, reproductive, histological, and lifestyle information for analysis.

Research Scope

The study used all primary cases of breast cancer in adult females, age 18 and over, living in Kentucky between years 2004 and 2007.

Study Population

The study population included all female breast cancer cases in Kentucky from 2004-2007. The original sample included 11,822 breast cancer records in the female population of 8,543,939 at risk (Kentucky Cancer Registry [KCR], 2011). Women that

died due to accidental events not associated with medical diagnosis were excluded from this study and thus, did not contribute to case analysis. After excluding cases not meeting parameters of the study project, 11,814 cases were used for the statistical analysis. The final study population included 8642 Non-Appalachian and 3172 Appalachian women.

Statistical Analysis

This study used SPSS ® Version 20 to assess breast cancer mortality among adult females with breast cancer living in Kentucky between 2004 and 2007. Descriptive statistics and chi-square analyses were calculated to compare ethnicity, residence, tobacco use, number of live births, and estrogen and progesterone receptor tumor status between the Appalachian and Non-Appalachian region of Kentucky. Separate adjusted and unadjusted multivariate logistic regression models were constructed for parity, region, and tumor receptor status. Mortality was considered the dependent variable. The full model adjusted for age, ethnicity, tumor status, tumor grade, tumor stage, family history, tobacco use, and menopausal status. An additional multivariate logistic regression model used backward elimination to analyze the interactions of the full-adjusted model.

Number of live births, the main variable, was divided into 5 categories --- 0, 1, 2, 3 and 4 or more live births (Whiteman et al., 2004). Tobacco use was categorized as "yes tobacco use" or "no tobacco use," considering cigarette, cigar, and chewing tobacco history. Tumor grade was categorized according to the clinical TNM stage grouping from the cTNM classification using the *AJCC Cancer Staging Manual* as tumor grade I, II, III, and IV (KCR, 2011). Tumor stage was coded according to Kentucky Cancer Registry's coding protocol using coding guidelines in Appendix C of the SEER Program Coding

and Staging Manual (KCR, 2011). Tumor stage was further categorized as "early stage" and "late stage." Tumors that were "SEER Stage I" and "SEER Stage II" were considered "early stage." Tumors that were advanced past SEER Stage II were considered "late stage" (Huang, et al., 2009). Race was categorized as white, or non-white (McDavid, et al., 2003). Recurrence was categorized as recurred or non-recurring breast cancer. Estrogen receptor and Progesterone receptor tumor status was considered positive or negative. An additional variable, age at diagnosis, was created subtracting date of birth from date of diagnosis (Albrektsen, et al., 2010). Tumor behavior was considered invasive or in-situ. Family history, number of primaries, and menopausal status were also included in the model. Postmenopausal status was assumed for incomplete data fields with age greater than or equal to 65 years old. The entire data set was received from the Kentucky Cancer Registry stratified by region according to residence in the Appalachian and Non-Appalachian region of Kentucky. Appalachian counties were designated by the Kentucky Cancer Registry as the 52 following counties: Adair, Bath, Bell, Boyd, Breathitt, Carter, Casey, Clark, Clay, Clinton, Cumberland, Elliott, Estill, Fleming, Floyd, Garrard, Green, Greenup, Harlan, Jackson, Johnson, Knott, Knox, Laurel, Lawrence, Lee, Leslie, Letcher, Lewis, Lincoln, Madison, Magoffin, Martin, McCreary, Menifee, Metcalfe, Monroe, Montgomery, Morgan, Nicholas, Owsley, Perry, Pike, Powell, Pulaski, Robertson, Rockcastle, Rowan, Russell, Wayne, Whitley, Wolfe.

This study used a cross-sectional observational epidemiologic framework. The data supplied by the Kentucky Cancer Registry provided demographic, reproductive, histological, and lifestyle information for analysis.

CHAPTER FOUR

Results

Demographics

Demographic characteristics for the breast cancer registry patients in Kentucky are listed in Table 1.   From 2004 – 2007, 93.3% of the population was white with 26.8% of women with breast cancer in Kentucky were living in the Appalachian region and 73.20% living in the Non-Appalachian region of Kentucky.   The mean age of diagnosis was 61.03 years of age. Progesterone receptor-positive and estrogen receptor tumor status was predominantly positive with 64.2% and 75.9%, respectively. More than 60% of the women were non-smokers. The number of live births for women with breast cancer in Kentucky was 12.8%, 19.9%, 32.6%, 18.8%, and 15.8% for no live births, one, two, three, and four or more live births, respectively.

Table 1. Demographic Characteristics of Breast Cancer Registry Patients in Kentucky, 2004-2007.

	Mean (SD) or Percentage
Ethnicity	
White	93.3%
Non-White	6.8%
Age	61.03 (13.84)
Residence	
Appalachia resident	26.8%
Non-Appalachia resident	73.2%
Progesterone Receptor	
PR+	64.2%
PR-	35.8%
Estrogen Receptor	
ER+	75.9%
ER-	24.4%
Tobacco Use	
No	60.7%
Yes	39.3%
Number of Live Births	
0	12.8%
1	19.9%
2	32.6%
3	18.8%
4 or greater	15.8%

The data in Table 2 show that one live birth and three live births significantly increases an adult woman's risk of breast cancer mortality by 91% and 58%, respectively, after adjusting for age, ethnicity, tumor status, family history, tobacco use, tumor grade, menopausal status, tumor behavior, tumor stage, and region in Kentucky. Before adjusting for these factors, one, two, and three live births were not significant in predicting mortality among adult women living in Kentucky during 2004 and 2007. However, four or more live births did show a significant 57% increase in breast cancer mortality. The adjusted and unadjusted models had an overall p-value <.001.

Table 2. Number of Live Births and Odds Ratio of Breast Cancer Mortality among Adult Women in Kentucky, 2004-2007.

Parity	No. of cases	No. of non-cases	OR unadjusted	95% CI	OR adjusted	95% CI
0	104	619	REF		REF	
1	193	927	1.24	0.96-1.61	1.91**	1.20-3.00
2	223	1612	0.82	0.64-1.06	1.21	0.78-1.86
3	156	903	1.03	0.79-1.35	1.58*	1.00-2.50
4+	186	704	1.573**	1.21-2.05	1.41	0.89-2.23

0 live births is reference

Abbreviations: CI, Confidence Interval; OR, Odds Ratio

* p <0.05   ** p <0.01

Adjusted for age, ethnicity, ER/PR, family history, tobacco use, recurrence, menopausal status, region, tumor grade, stage, and behavior.

Tumor Receptor Status

The data in Table 3 show that progesterone receptor-negative tumor status significantly increases an adult woman's risk of breast cancer mortality by 64% after adjusting for age, ethnicity, tumor status, family history, tobacco use, tumor grade, parity, menopausal status, tumor behavior, tumor stage, and region in Kentucky. Estrogen receptor status was not a significant predictor in the adjusted model. Both estrogen receptor and progesterone receptor-negative status was associated with a significant increase in a woman's risk for breast cancer mortality between 2004 and 2007, unadjusted for other covariates. A backwards elimination logistic regression model showed a significant interaction between Appalachia and progesterone receptor tumor status. The resulting odds ratio of the interaction model showed a 3.13 fold increase in breast cancer mortality for a woman with progesterone receptor-negative breast cancer living in the Appalachian region compared to a women with progesterone receptor-negative in the Non-Appalachian Kentucky between 2004 and 2007. The adjusted and unadjusted models had an overall p-value <.001.

Table 3. Receptor Type and Odds Ratio of Breast Cancer Mortality of Adult Women in Kentucky, 2004-2007.

	No. cases	No. non-cases	OR unadjusted	95% CI	OR-adjusted	95% CI
Estrogen receptor (-)	1060	6606	1.30**	1.11-1.53	1.07	0.74-1.54
Progesterone receptor (-)	818	5585	1.72**	1.48-2.00	1.64**	1.18-2.28

Reference is (+) for each level of hormone

Abbreviations: CI, Confidence Interval; OR, Odds Ratio

* p <0.05, ** p <0.01

Adjusted for age, ethnicity, tumor status, family history, tobacco use, tumor grade, tumor stage, recurrence, menopausal status, parity, region

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Regional Differences

      The data in Table 4 show that women with breast cancer living in the Appalachian region of Kentucky between 2004 and 2007 have a 1.23 fold unadjusted and 3.14 fold adjusted increase in breast cancer mortality risk compared to women with breast cancer in Non-Appalachia.   A Pearson's chi-square confirmed the mortality rate among women in Kentucky with breast cancer was significantly different with a 19.6% mortality rate in the Appalachian region, compared to 16.6% mortality rate in the Non-Appalachian region of Kentucky. The mortality difference is consistent with the literature and government statistics (Halverson et al., 2004).

Table 4. Residence in Kentucky and Odds Ratio of Breast Cancer Mortality among Adult Women in Kentucky, 2004-2007.

	No. cases	No. non-cases	OR unadjusted	95% CI	OR-adjusted	95% CI
Appalachia	1431	7211	1.23**	1.11-1.37	3.14*	1.10-8.91

Reference is Non-Appalachia Residence

Abbreviations: CI, Confidence Interval; OR, Odds Ratio

* p <0.05   ** p <0.01

Adjusted for age, ethnicity, ER/PR, family history, tobacco use, recurrence, menopausal status, parity, tumor grade, stage, and behavior.

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CHAPTER FIVE

Discussion

The purpose of this study is to investigate the breast cancer mortality rate differences among women living in the Appalachian and Non-Appalachian regions of Kentucky. Specifically, the research questions aimed to determine if the breast cancer mortality rate was increased in the Appalachian region of Kentucky due to a more aggressive subtype of breast cancer or other socioeconomic, reproductive, or lifestyle factors.

The limitations of this study should be considered when interpreting the results. This cross-sectional study is subject to several limitations. First, this study analyzed adult women with breast cancer living in Kentucky between 2004 and 2007. Therefore, the results cannot be extrapolated to women without breast cancer, females under the age of 18, men with breast cancer, or women living outside of Kentucky between 2004 and 2007. Next, additional factors to define lifestyle, reproductive, and socioeconomic status were not analyzed in the model. Thus, BMI, education, income, environment, genetic sequences, age at first pregnancy, age at first menstrual cycle, nutritional status, dietary consumption, and other undefined factors were not included in this model. Yet, the main impediment to this research is the degree of missingness of the main variable parity. In addition, excluded incomplete records were more likely to be collected from the Appalachian region, which may have also biased the results. However, multiple imputations of all variables with logistic regression, excluding parity, justified the selection of the original model.

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The first research question asked if the number of live births had an effect on the breast cancer mortality variation among adult women with breast cancer living in Kentucky. The researcher initially expected parity to be negatively associated with mortality. However, the data contradicted this hypothesis. After further review of literature, the researcher found a majority of the previous research to investigate parity with breast cancer incidence instead of mortality. Few studies have examined the association of parity after a woman has been diagnosed with breast cancer. An article in 2009, highlighted this discrepancy and concluded women with four or more children, using data from a Swedish Cancer Registry, were found to have a poorer prognosis compared to women with one live birth (S. Butt et al., 2009). Further review found a similar study in U.S. women to yield results concluding parity increases a woman's risk of breast cancer mortality (Whiteman, et al., 2004). Possible explanations for this result would be explained by an enhanced initiation of breast cancer proliferation related to pregnancy (Butt, Borgquist, Anagnostaki, Landberg, & Manjer, 2009; Butt, et al., 2009; Whiteman, et al., 2004). During a woman's lifetime, endogenous hormones oscillate according to menstrual cycle and pregnancy (Butt, et al., 2009; Ursin et al., 2005). These endogenous hormones may have an effect on the proliferation of breast cancer cells by providing a susceptible physiological state for abnormal cell proliferation (Butt, et al., 2009; Ursin, et al., 2005). On the other hand, non-hormonal influences that have not been suppressed by the protective effect of parity may also affect the rate of mortality (Phipps, et al., 2011; Whiteman, et al., 2004). In addition, factors such as BMI related to increased adipose tissue, menopausal status, and oral contraceptive use may contribute to risk estimates observed. However, the exact effect of parity on the initiation and

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pathology of breast cancer mortality is still unclear and cannot be defined by this research study. Thus, more invasive research is needed.

The second research question asked if breast cancer tumor receptor status had an effect on mortality in women with breast cancer living in Kentucky. This study found progesterone receptor-negative status to be significantly associated with breast cancer mortality in Kentucky. Furthermore, after adjusting for the other variables and the interaction term the study found a significant increase in breast cancer mortality for a woman with progesterone receptor-negative breast cancer versus progesterone receptor-negative breast cancer living in the Appalachian region of Kentucky between 2004 and 2007. The researcher did not expect to see the degree of increased risk related to region as observed by the data. Progesterone receptor-negative status is a very aggressive tumor subtype characterized to have a poor prognosis (Lari et al, 2011; Phipps et al, 2011). These results raise the question if this aggressive tumor subtype's poor prognosis is exacerbated by poor socioeconomic status, as observed in the Appalachian region of Kentucky or is there additional unknown cofounders that have not been investigated?

The third research question asked what factors contribute to the mortality difference between the Appalachian and Non-Appalachian region in women with breast cancer living in Kentucky. A logistic regression model concluded a significant increase in breast cancer mortality in the Appalachian region of Kentucky. Progesterone receptor status and number of primaries were the most significant in predicting mortality in this population. Literature supports these findings (Smigal, et al., 2006; Ursin, et al., 2005). However, a backwards elimination regression model selecting for interactions between region versus parity, menopausal status, age at diagnosis, family history, tumor behavior,

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recurrence, and ethnicity were not significant. This may be due to the large amount of missingness in the data or the small population size of women with breast cancer in years 2004 to 2007, versus a larger selection of years. In addition, other risk factors such as BMI, education, income, insurance, and travel distance were not included in this model, which could have been factors in the increased mortality rates. Therefore, this data cannot reliably provide enough evidence to define the breast cancer mortality rate differences between the two regions. Instead, this data can only confirm that there is a difference in mortality between the two regions and that more research is necessary to define these interactions.

CHAPTER SIX

Conclusion

This study concluded reproductive differences and estrogen receptor tumor status between the Appalachian and Non-Appalachian region of Kentucky do not contribute to the difference in mortality between the two regions. However, progesterone receptor tumor status did provide evidence to suggest aggressive tumor receptor subtype differences may contribute to the regional mortality variation. Progesterone receptor-negative subtype, an aggressive form of breast cancer, was the most indicative predictor of breast cancer mortality in adult women living in the Appalachian region of Kentucky. This suggest women in the Appalachian region are more likely to die of breast cancer if they have progesterone receptor-negative breast cancer than if they live the Non-Appalachian region of Kentucky. However, progesterone receptor-negative status may also have addition socioeconomic influences that were not included in the risk assessment.

The results of this study provide some epidemiological evidence that parity, receptor subtype, and socioeconomic factors are involved in the risk of breast cancer mortality. Limited research has investigated breast cancer mortality among Kentucky women, specifically between the Appalachian and Non-Appalachian regions of Kentucky. In comparison to previous studies that focused on risk assessment of parity to incidence of breast cancer, this study analyzed the effect of parity on the risk of breast cancer mortality. This study provided support for the novel research associating increased parity to be positively associated with breast cancer mortality. In addition, this study provided support to infer poor socioeconomic factors, associated with the

Appalachian region, provide the poorest prognosis for a woman with breast cancer in Kentucky. Socioeconomic, as well as environmental and lifestyle factors unique to the Appalachian region such as lower high school graduation rates, increased obesity rates, decreased access to healthcare, delayed diagnoses, and poor nutritional statuses may pose a significant risk of breast cancer mortality in these Kentucky women.

These findings have important implications for developing educational, preventative, and research techniques to decrease mortality in both the Appalachian and Non-Appalachian regions of Kentucky.   Prevention efforts should be aimed at addressing and improving socioeconomic factors, increasing access to health care, and continued efforts researching the breast cancer risk factors among Kentucky women. Early mammograms should be encouraged by establishing funding from organizations to provide free mammograms in socioeconomically deprived areas of Kentucky.   In addition, Kentucky can take strides to improve cancer registry data quality by encouraging hospitals to record accurate and complete data records. This would decrease the amount of missingness in the cancer registry data. Furthermore, a cancer registry database could be developed to include dietary, lifestyle, and socioeconomic data. This database would provide a comprehensive tool for researchers to better define risk factors associated with breast cancer.

Future investigation is needed to better establish risk assessment models incorporating socioeconomic, reproductive, and lifestyle factors to aid in the prevention of breast cancer mortality in Kentucky women. Prospective studies should compare breast cancer data between Area District Development Regions to better categorize socioeconomic influences. Current research also shows nutritional status may prove to

be an important predictor in the vital status of breast cancer. The proposed research should analyze Kentucky breast cancer medical data against dietary and socioeconomic data. Future research efforts are warranted to define the relationship between dietary intake and subtypes by controlling for socioeconomic factors. In conclusion, socioeconomic influences related to nutritional status, lifestyle factors, and reproductive factors are an important topic for further study.

APPENDICES

Appendix A: IRB Approval Documentation

UK
UNIVERSITY OF
KENTUCKY

Office of Research Integrity
IRB, IACUC, RDRC
315 Kinkead Hall
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EXEMPTION CERTIFICATION

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MEMO: Kara Hagan,
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FROM: Institutional Review Board
         c/o Office of Research Integrity

SUBJECT: Exemption Certification for Protocol No. 11-0296-X1B

DATE: April 13, 2011

On April 12, 2011, it was determined that your project entitled, *Breast Cancer trends among Kentucky women*, meets federal criteria to qualify as an exempt study.

Because the study has been certified as exempt, you will not be required to complete continuation or final review reports. However, it is your responsibility to notify the IRB prior to making any changes to the study. Please note that changes made to an exempt protocol may disqualify it from exempt status and may require an expedited or full review.

The Office of Research Integrity will hold your exemption application for six years. Before the end of the sixth year, you will be notified that your file will be closed and the application destroyed. If your project is still ongoing, you will need to contact the Office of Research Integrity upon receipt of that letter and follow the instructions for completing a new exemption application. It is, therefore, important that you keep your address current with the Office of Research Integrity.

For information describing investigator responsibilities after obtaining IRB approval, download and read the document "PI Guidance to Responsibilities, Qualifications, Records and Documentation of Human Subjects Research" from the Office of Research Integrity's Guidance and Policy Documents web page [http://www.research.uky.edu/ori/human/guidance/htm#PIresp]. Additional information regarding IRB review, federal regulations, and institutional policies may be found through ORI's web site [http://www.research.uke.edu/ori]. If you have questions, need additional information, or would like a paper copy of the above mentioned document, contact the Office of Research Integrity at (859) 257-9428.

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Appalachian region of Kentucky – 52 counties in the state of Kentucky which include

Adair, Bath, Bell, Boyd, Breathitt, Carter, Casey, Clark, Clay, Clinton, Cumberland,

Elliott, Estill, Fleming, Floyd, Garrard, Green, Greenup, Harlan, Jackson, Johnson, Knott,

Knox, Laurel, Lawrence, Lee, Leslie, Letcher, Lewis, Lincoln, Madison, Magoffin,

Martin, McCreary, Menifee, Metcalfe, Monroe, Montgomery, Morgan, Nicholas,

Owsley, Perry, Pike, Powell, Pulaski, Robertson, Rockcastle, Rowan, Russell, Wayne,

Whitley, Wolfe (Kentucky Cancer Registry, 2011)

Nulliparity – Zero live births of a woman (Salma Butt, et al., 2009)

Number of live births – Refers to the actual number of offspring born alive. (Kentucky

Cancer Registry, 2011)

Number of primaries - Number of recorded primary cancer sites (Kentucky Cancer

Registry, 2011)

Parity – Number of live children born from a woman (Salma Butt, et al., 2009; Ursin, et

al., 2005)

Tumor-receptor – protein biological marker on the surface of a cancer cell (Bernstein &

Lacey, 2011; Jerry, et al., 2010; Lari & Kuerer, 2011)

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