2019

Disparities in the risk of subsequent primary cancer diagnosis and recurrence among women with breast cancer (first primary) in Kentucky

Pierre Fwelo
University of Kentucky, fwelo.pierre@uky.edu

STUDENT AGREEMENT:

I represent that my capstone and abstract are my original work. Proper attribution has been given to all outside sources. I understand that I am solely responsible for obtaining any needed copyright permissions. I have obtained needed written permission statement(s) from the owner(s) of each third-party copyrighted matter to be included in my work, allowing electronic distribution (if such use is not permitted by the fair use doctrine) which will be submitted to UKnowledge as Additional File.

I hereby grant to The University of Kentucky and its agents the irrevocable, non-exclusive, and royalty-free license to archive and make accessible my work in whole or in part in all forms of media, now or hereafter known. I agree that the document mentioned above may be made available immediately for worldwide access unless an embargo applies.

I retain all other ownership rights to the copyright of my work. I also retain the right to use in future works (such as articles or books) all or part of my work. I understand that I am free to register the copyright to my work.

REVIEW, APPROVAL AND ACCEPTANCE

The document mentioned above has been reviewed and accepted by the student's advisor, on behalf of the advisory committee, and by the Director of Graduate Studies (DGS), on behalf of the program; we verify that this is the final, approved version of the student's capstone including all changes required by the advisory committee. The undersigned agree to abide by the statements above.

Pierre Fwelo, Student

Dr. Steve Fleming, Committee Chair

Dr. Sarah Wackerbarth, Director of Graduate Studies

Disparities in the risk of subsequent primary cancer diagnosis and recurrence among women with breast cancer (first primary) in Kentucky (2004-2016)

CAPSTONE PROJECT PAPER

A paper submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

In the

University of Kentucky College of Public Health

By

Pierre Fwelo

Lexington, Kentucky

April 16, 2019

Committee Members

_____

Steve Fleming, PhD – Chair

_____

Robin Vanderpool, DrPH

_____

Jaclyn McDowell, DrPH

CONTENTS

I. ABSTRACT

Background and objectives

Breast cancer is one of the most common malignancies among women in the United States. Women residing in the state of Kentucky have breast cancer incidence and mortality rates greater than the national average. Recent studies suggest an association between breast cancer subtypes/hormone receptor (HR) status and the risk of recurrence and the onset of subsequent primary cancer, however, limited research has focused on Kentucky or its Appalachian region. Investigating these associations may potentially save lives by providing information that can be used in breast cancer education in Kentucky, assessing the population at greater risk of recurrence and subsequent cancer (by subtypes), increasing screening in the population at risk, and developing tailored interventions for each region. Therefore, the purpose of this study was to examine the relationship between breast cancer subtypes/hormone receptor status and the risk of recurrence and/or the risk of subsequent cancers among women in Kentucky with a specific focus on disparities in these risks that may exist between women living in Appalachia compared to non-Appalachia.

Methods

The analysis used data from the Kentucky Cancer Registry (KCR), specifically females ages 18 or older diagnosed with primary breast cancer between 2004 and 2016. A retrospective cohort study was conducted to assess the risk of (1) subsequent primaries and (2) recurrence among each breast cancer subtype/HR status. Subjects' maximum follow-up period for the cohort study

was five years or 60 months. To assess the relationship between breast cancer subtypes and the risk of recurrence and/or the risk of subsequent cancers, a series of Cox regression analyses were performed. The study was conducted in two parts: first, we analyzed data from women diagnosed between 2004 and 2016, examining HR status as a risk factor and second, we focused on women diagnosed between 2011 and 2016, examining breast cancer subtype as a risk factor.

Results

Between 2004 and 2016, it was observed that women with estrogen receptor-positive (ER+ only) breast cancer had a lower risk of subsequent primaries compared to women with HR+ (estrogen receptor-positive [ER+] and progesterone receptor-positive [PR+]) breast cancer (HR:0.85, 95% CI: 0.74,0.96). When stratified by Appalachian status, a similar trend was only seen among non-Appalachian women (HR:0.80, 95% CI: 0.69,0.94). In examining recurrence outcomes, women with ER+, PR+, and HR-negative (HR-) breast cancer had an increased risk compared to women with HR+ breast cancer with hazard ratios of 1.61 (1.28, 2.03), 2.09 (1.57,3.96), and 3.16 (2.64, 3.79), respectively. Clinically significant disparities in the risk of recurrence between Appalachian and non-Appalachian women were also observed for ER+ (1.49 vs. 1.84), PR+ (2.47 vs 2.30), and HR- (2.07 vs. 2.58) breast cancer subtypes. For the focused analysis (2011-2016), women with Luminal A and B subtypes had a lower risk of recurrence compared to human epidermal growth factor receptor 2 (HER2) enriched and triple negative in both the

overall and stratified analyses. Also, non-Appalachian women with Luminal B had a reduced risk of subsequent cancers (HR:0.76, 95% CI: 0.59,0.99) compared to non-Appalachian women.

Conclusion

Among this population-based sample of women in Kentucky, breast cancer subtype/HR status was associated with the risk of subsequent primaries and recurrence. There were also noted disparities in the risk of recurrence between women who live in Appalachian Kentucky and women living in non-Appalachia. Women living in Appalachian Kentucky tended to have lower risk of recurrence compared to women living in non-Appalachia for similar subtypes adjusted for several clinical, behavioral, and insurance-related variables.

II. Introduction

Breast cancer is a disease that is characterized by the proliferation of malignant breast cells. It is the most common malignancy in women worldwide, and the most common cause of cancer-related death among women. It is estimated that 2.1 million new cases and 626,679 deaths will occur worldwide in 2018 [1]. In the United States (U.S.), breast cancer is the most common type of cancer and the second most common cause of death; specifically, in 2018 is estimated that there will be 266,120 new cases of female breast cancer and 40,920 deaths will occur as a result of the disease [2]. Although the exact cause of breast cancer is unknown, multiple risk factors have been associated with its development including tobacco use, diet, alcohol use, age at menarche, parity, breast feeding, age at menopause, and endogenous hormones [3-6].

Breast cancer is often subdivided into four main molecular subtypes based on the genes expressed by the malignant breast cells: Luminal A, Luminal B, human epidermal growth factor receptor 2 (HER2) enriched, and basal-like (triple negative) [7,8]. Luminal A subtype is characterized by positive hormone receptors (HR) (estrogen-receptor [ER] and/or progesterone-receptor [PR]), negative HER2, and low levels of the protein Ki-67. Luminal B subtype is characterized by positive HR (ER+ and/or PR+), and either HER2 positive or HER2 negative with high levels of Ki-67 [9]. A cancerous breast cell is considered HER2-enriched or overexpressed when it is HR negative (ER- and PR-) and HER2 positive [10]. The triple negative subtype is characterized by HR negative cancerous breast cells (ER- and PR-) and negative HER2 [11,12].

Recent studies suggest an association between breast cancer subtype/hormone receptor status and outcomes such as recurrence and subsequent primaries[13-16]. Most of these studies have involved nationwide or global analyses, which can introduce ecological fallacies [17,18]. Few studies have investigated the association in specific U.S. states or among specific geographic, medically underserved populations such as Appalachian Kentucky. In addition, current studies have only focused on contralateral breast cancer as a subsequent cancer rather than any other type of subsequent cancers [13,14]. Therefore, this study aimed to examine the relationship between breast cancer subtypes and the risk of recurrence and/or the risk of any subsequent cancers in the state of Kentucky. Furthermore, the study investigated the potential disparities in these risks between women living in the 54-county, primarily rural Appalachian region of the state compared to women residing in non-Appalachia (66 counties). Based on rural-urban continuum codes,

Kentucky is approximately 40% rural, compared to the Appalachian region, which is over 80% rural [19-22]. Rural women in the state have notable breast cancer disparities (e.g., increased mortality, late stage diagnoses) compared to non-rural women. These disparities may be due to geographic isolation, high prevalence of poverty, barriers to healthcare and mammography services (e.g., transportation, educational ascertainment / literacy, social support, stigma) [20,22,23]. Exploring the impact of breast cancer subtypes on the outcomes of interest may further explain the breast cancer inequities observed in the Appalachian region.

LITERATURE REVIEW

The following review is a synopsis of the current knowledge of the association between breast cancer subtype/hormone receptor status and recurrence and/or subsequent primary in the published literature. This review gathers empirical and theoretical knowledge from peer-reviewed journal articles, books, governmental fact sheets, websites, and national and international organizational reports in the field of epidemiology, medicine, oncology, public health, and physiology. Relevant literature was found through the following databases: Google Scholar, Web of Science, and PubMed using keywords or phrases such as *breast cancer, breast cancer recurrence, breast cancer subtypes, multiple primary, Appalachia, Kentucky* and *subsequent cancer.* Additional material cited in relevant works was included in the literature review. The literature review is divided into the following sections: breast cancer, subtypes, recurrence and subsequent primary tumors, and breast cancer in Kentucky.

Breast cancer

Breast cancer refers to malignant or compromised cell proliferation originating from breast tissue [3,24]. Breast cancer usually originates from the lobule, the gland the makes milk (lobular carcinoma) or the inner lining of milk ducts, a thin tube that carries milk from the breast lobule to the nipple (ductal carcinoma) [25-28]. Breast cancer cells can metastasize through the bloodstream, channels to nearby lymph nodes, and/or invade regional and distant organs [24,29]. Breast cancer starts the carcinogenesis process by the random and/or induced (e.g., electromagnetic or nuclear radiation, viruses, environmental exposure, biological hazards or food) modification or mutation of normal cells' DNA, RNA, tumor suppressor genes, DNA repair genes, and/or the creation of oncogene (from proto-oncogenes) [30].

Oncogenes and tumor suppressor genes are the two principal genes that play a major role in the carcinogenesis process. Oncogenes are mutated proto-oncogenes (i.e., normal proteins involved in cell cycle progression) that are abnormally active and induce proliferation. Tumor suppressor genes regulate or inhibit the proliferation of normal and mutated cells by slowing down cell division, repairing DNA mistakes, or ordering cells to die (a process known as *apoptosis* or *programmed cell death*) [31-33]. When tumor suppressor genes and/or proto-oncogenes of normal cells are mutated, the neoplastic cells acquire the ability to continuously proliferate, evade apoptosis, grow with unlimited potential, evade the immune system, and become independent from growth factors or metastasize [34]. HER2, Breast Cancer type 1 susceptibility protein (BRCA1), Breast Cancer type 2 susceptibility protein (BRCA2), and p53 are examples of oncogenes and tumor suppressor genes that play a major role in breast cancer carcinogenesis.

Subtypes

Breast cancer is classified into four main molecular subtypes that are based on the protein expressed by the neoplastic cells. The molecular subtypes include Luminal A, Luminal B, HER2 enriched, and triple negative. These breast cancer subtypes play a major role in the cancer's virulence, growth, metastatic ability, and responsiveness to treatment [7,9-11].

Luminal A breast cells are characterized by the presence of steroid HR (estrogen and/or progesterone), meaning that the cancerous cells grow faster in the presence of estrogen or progesterone. In addition, Luminal A cells have a normal amount or no HER2. Lastly, Luminal A cells have a low expression of antigen Ki-67, a protein that indicates how fast cells are dividing. Luminal A cells tend to grow slowly, be less aggressive, and have low recurrence rates. They are also more responsive to endocrine treatments, thus people with Luminal A breast cancer tend to have a high survival rate [35]. Luminal B breast cancer cells are also HR+, but differ from Luminal A breast cancer cells by the presence of an excessive amount of HER2. Neoplastic cells can also be categorized as Luminal B when they are HR+, have a normal amount or no HER2, and have high Ki67 level. Luminal B breast cancers have a significantly higher proliferation rate and worse prognosis than Luminal A [36]. HER2 enriched or overexpressed breast cancer cells are HR-, meaning the neoplastic cell growth is not triggered or enhanced by the presence of estrogen or progesterone, and have an excessive amount of HER2. They grow and spread more aggressively than Luminal A and B subtypes. HER2 enriched breast cancer

cells are also more likely to be high grade and node positive than the Luminal subtypes[37]. Basal like or triple negative are breast cancer cells that are both HR- and HER2 negative. They have a high histologic grade, are very aggressive, and have the worst prognosis of all subtypes [11,12]. Numerous studies have linked breast subtype to the risk of recurrence and/or second primary [15,16].

Recurrence

Cancer recurrence refers to the reemergence of a cancer after a period of remission. It is potentially caused by the survival of a small number of cancerous cells after treatment that may not show up in tests during the remission period. The Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute (NCI) considers a new cancer of the same site or with the same histology as an earlier one as the same primary cancer if diagnosed within 60 months, unless the medical record specifically states that it is recurrent or metastatic disease (https://seer.cancer.gov/tools/mphrules/mphrules_flowchart.pdf). Cancer recurrence can be local (in or around the initial location), regional (in the lymph nodes or tissue near initial cancer), or distant (in organs and far from the initial location) [38]. Current studies have investigated and established an association between breast cancer subtypes and the risk of breast cancer recurrence [15,16]. Luminal A tumors are associated with the lowest risk of recurrence rates while basal-like tumors have the highest risk; Luminal B and HER2 have intermediate risks [15,16,37,39-42].

Subsequent Primary Tumors

A subsequent primary tumor is a new, unrelated, and histologically different primary cancer in a person who has a previously diagnosed cancer. Among women with breast cancer as a first primary cancer, the incidence of multiple primaries has been reported in the range of 4.1% [43] to 16.4% [44]. Recent epidemiologic studies have suggested an association between breast cancer HR status and the risk of subsequent primary tumors [13,14]. One relevant study used the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) database to examine the risk of a second primary (contralateral breast cancer) among 4,927 women diagnosed with a first primary breast cancer between 1992 and 2004. The exposure and outcome of interest were HR status and the risk of contralateral breast cancer, respectively. The study found that women with a first primary HR+ breast tumor had an elevated risk of contralateral primary breast cancer compared to the general population adjusted for age, race, and calendar year (SIR = 2.22, 95% CI = 2.15, 2.29). Also, women with HR- breast tumors had a statistically significantly higher risk of a second contralateral breast cancer diagnosis than women with HR+ breast tumors (SIR = 3.57, 95% CI = 3.38, 3.78) [14]. The vast majority of literature available on the association between HR status and subsequent primary cancers has focused on contralateral breast cancer as the subsequent cancer [13,14]. Few have looked at the risk of any other subsequent cancers. There is a need to further investigate the potential association between breast cancer

subtypes and the risk of either breast cancer recurrence or subsequent primary cancer. This study will provide additional elucidation on this association by focusing on the state of Kentucky.

Breast cancer in Kentucky

The age-adjusted incidence rate of invasive female breast cancer in Kentucky during 2012-2016 is 126.3 per 100,000 (Figure 1). The incidence rate was different by Appalachia status. In Kentucky's Appalachian region, the incidence rate was 118.1/100,000 [95% CI: (114.5, 121.7)], while in Kentucky's non-Appalachian region the rate was 129.4/100,000 [(95% CI: (127.1,131.98)] in the same period. Furthermore, the incidence of Luminal A breast cancer in Kentucky's Appalachian region was 73.9/100,000 [95% CI: (70.8, 77.1)], while in Kentucky's non-Appalachian region the rate was 86.0/100,000 [(95% CI: (83.9,88.1)] (Figure 3). Luminal B breast cancer incidence rate in Kentucky's Appalachian region was 11.5/100,000 [95% CI: (10.2,12.8)], while in Kentucky's non-Appalachian region the rate was 12.5/100,000 [(95% CI: (11.7,13.3)] (Figure 4). HER2-enriched breast cancer incidence rate in Kentucky's Appalachian region was 5.6/100,000 [95% CI: (4.7,6.5)], while in Kentucky's non-Appalachian region the rate was 5.3/100,000 [(95% CI: (4.8,5.9)] (Figure 5). Triple negative breast cancer incidence rate in Kentucky's Appalachian region was 15.4/100,000 [95% CI: (14.0,17.0)], while in Kentucky's non-Appalachian region the rate was 14.3/100,000 [(95% CI: (13.5,15.2)] (Figure 6).
Although the overall incidence rate of female breast cancer is lower in Appalachian Kentucky as compared to non-Appalachian Kentucky, the mortality rate is higher. The mortality rate among non-Appalachian women was 20.7/100,000 (95% CI: (19.1,21.7) versus 23.2/100,000 (95% CI: (21.5,25.1) among Appalachian women (Figure 2). Lower breast cancer incidence and higher mortality rates in Appalachian KY may be explained by documented risk factors and inequities

in social determinants of health among Appalachian populations such as geographic isolation, access to care barriers, (e.g., transportation, under or uninsured, educational ascertainment / literacy, social support, stigma), poor quality of life outcomes, cultural beliefs, significant socioeconomic barriers, later stage diagnoses, co-morbidities, and/or under-screening [20-23,45].

III. METHODS

Study Design

This study is a retrospective cohort focused on women diagnosed with invasive breast cancer as a first primary between 2004 and 2016 in Kentucky using KCR data. Study subjects were followed for a maximum of 60 months from the date of the diagnosis of the first primary to the onset of a subsequent primary cancer diagnosis and the recurrence of the first primary. The study sample was then stratified by Appalachian status (Appalachian vs. non-Appalachian based on county of residence; https://www.arc.gov/appalachian_region/CountiesinAppalachia.asp) to observe its impact on the distribution of the exposure of interest (breast cancer subtypes) and the outcomes of interest (recurrence and subsequent primary cancer). The study was limited to breast cancer cases among women ages 18 years or older with known HR status (estrogen and/or progesterone receptors). Breast cancer cases diagnosed at autopsy or death certificate only were excluded from the cohort. 41,391 women were diagnosed with malignant breast cancer (first primary) between 2004 and 2016 in Kentucky. From this sample, 31,058 satisfied the inclusion criteria and composed the analytic cohort. 8,150 women resided in Appalachia and 22,908 resided in non-Appalachia.

Data Source

This study used KCR data from women ages 18 years or older diagnosed with a primary malignant breast cancer between 2004 and 2016. KCR is the official population-based cancer registry of the Commonwealth of Kentucky, part of NCI's SEER program, and a longstanding member of the Centers for Disease Control and Prevention's National Program of Cancer Registries. KCR performs ongoing systematic collection, analysis, and interpretation of population-based cancer data in the state of Kentucky. More information about KCR can be obtained at https://www.kcr.uky.edu/about.php.

Demographic Covariates

The demographic characteristics of the cohort were composed of well-studied risk factors for cancer in general, and breast cancer in particular, such as age at diagnosis, stage of the first primary, race, tobacco use, family history (of the first primary), menopausal status, and insurance type. Age at diagnosis was categorized as follows: <35 years, 35-44, 45-54, 55-64, 65-74, 75-84, and 85+). Stage at diagnosis of the first primary was categorized in four groups following SEER Summary Stage 2000 (localized, regional, distant, and unknown). Race was divided into black, white, other and unknown. Tobacco use, family history, and menopausal status each had three categories (Yes, No, and Unknown). Insurance status was categorized into not insured, insured (people with private, military, and/or veteran insurance), Medicaid, Medicare, and unknown.

Exposure Assessment

The exposure of most interest for this study was breast cancer subtypes. Because KCR lacked data on HER2 prior to 2009, the exposure of interest for women diagnosed with breast cancer between 2004 and 2016 was HR status (ER and PR). The study established four levels of exposure: ER+ only, PR+ only, ER+ and PR+, and ER- and PR-.

Breast cancer cases were categorized as **ER+ only** when cancerous breast cells grew faster in response to estrogen level only, **PR+ only** when cancerous breast cells grew faster in response to progesterone level only, **ER+ and PR+** when cancerous breast cells grew faster in response to both estrogen and progesterone levels, and **ER- and PR-** when cancerous cells grew independently of hormone level (progesterone or estrogen).

In the focused analysis, females diagnosed with breast cancer between 2011 and 2016, the exposure of interest was the combination of HR status and HER2 status, following the typical classification of breast cancer subtype. The subtypes were categorized independently of Ki67 levels because the KCR lacked data on this variable. The five levels of exposure for the focused analysis were Luminal A, Luminal B, HER2 enriched, triple negative, and other. Subjects were categorized as **Luminal A** when cancerous breast cells were ER+ and/or PR+, and HER-; **Luminal B** when cancerous breast cells were ER+ and/or PR+, and HER2+; **HER2 enriched** when cancerous breast cells were ER-, PR-, and HER2+; **triple negative** when cancerous breast cells were ER-, PR-, HER2-, and **Other** when cancerous breast cells had borderline results, missing one or more test(s), or not documented.

Outcome Assessment

The outcomes of interest of the study were: (1) the onset of subsequent primary cancer and (2) a recurrence within five years or 60 months from being diagnosed with breast cancer.

Statistical Analysis

All statistical analyses were performed using SAS version 9.4. Descriptive statistics of the relevant variable comparing Appalachian / non-Appalachian status were conducted using a t-test for continuous variables and chi-square for categorical variables. A series of univariate Cox proportional-hazard regressions were performed to assess the impact of potential cofounders and effect modifiers on the risk of subsequent cancer and recurrence. Multivariate Cox proportional-hazard regressions assessed the association between breast cancer cells HR status or subtypes with the hazard of subsequent cancer or recurrence by region of residence.

IV. RESULTS

ER/PR Status and Risk of Subsequent Primary Cancer and Recurrence (2004-2016)

The distribution of demographic characteristics was statistically different for women residing in Appalachia compared to women in non-Appalachia for the following variables: age at diagnosis, stage of the first primary, race, tobacco use, family history, menopausal status, number of live births, HR status, and insurance status (Table 1). In both geographic groups, whites were the majority (98.07% of Appalachian subjects were whites vs. 90.23% among non-Appalachian).

There was a higher prevalence of tobacco use among non-Appalachian residents than Appalachian residents (36.77% vs. 33.35%). Post-menopausal subjects were more prominent in non-Appalachia compared to Appalachia (65.03% vs. 60.97%). The prevalence of localized breast cancer was higher among non-Appalachian subjects compared to Appalachian subjects (64.57% vs. 60.87%). The distribution of health insurance coverage was noticeably different between the two geographic groups. Non-Appalachian subjects had a higher prevalence of private health insurance than Appalachian subjects (51.04% vs. 39.77%), while Appalachian subjects had a higher prevalence of Medicaid coverage (13.07% vs. 6.69%). Non-Appalachian residents had a higher burden of ER+ and PR+ tumors in the overall analysis (68.37% vs 66.44%) than Appalachia residents. The distribution of the outcome of interest (recurrence and subsequent cancer) was not statistically different between Appalachians vs non-Appalachians. After the 60 months follow-up period, 6% of the cohort were diagnosed with a recurrence of their first primary after remission and 8% had the onset of subsequent primaries with no statistically significant difference between the two geographic groups (Table 2). Breast cancer was the most common type of subsequent primary cancer among Appalachian residents (45.51%) and non-Appalachian residents (53.95%) (Table 3).

Univariate analysis results are provided in Table 4. Stage of the first primary, family history, menopausal status, age at diagnosis, tobacco use, and insurance status had positive associations with the risk of outcomes of interest ($p<0.05$). The multivariable Cox regression model results are shown in Table 5.

Subsequent primary

In the unstratified analysis (Appalachian + non-Appalachian), subjects who were **ER+ only** had a lower risk of subsequent cancer (HR:0.85, 95% CI: 0.74,0.96) than subjects who were **ER+**

and PR+. In the stratified analysis, non-Appalachian **ER+ only** subjects had a lower risk of subsequent cancer (HR:0.80, 95% CI: 0.69,0.94) compared to non-Appalachian subjects who were **ER+ and PR+**. Among Appalachian residents there were no statistically significant differences among subtypes.

Recurrence

For the recurrence outcomes, disparities in the risk associated with each subtype were observed. Compared to **ER+ and PR+,** Appalachian residents had the following increased hazard for **ER+ only**, **PR+ only,** and **ER- and PR-** (1.49, 2.47, 2.07, respectively). Non-Appalachian residents had the following increased hazard for **ER+ only**, **PR+ only** and **ER- and PR-**: 1.84, 2.30, 2.58, respectively.

ER/PR/HER2 Status and Risk of Subsequent Primary Cancer and Recurrence (2011-2016)

Part two of the study focused on women with breast cancer diagnosed between 2011 and 2016 and observed the impact of breast subtypes (HR + HER2 status). Non-Appalachian residents had a higher burden of Luminal A in the focused analysis (69.55% vs 66.12%) than Appalachia residents (Table 6). Table 7 lists the results of this focused analysis.

Recurrence

Compared to Luminal A subjects, Luminal B, HER2 enriched, and triple negative women had higher risks of recurrence with the following hazard ratios: 1.61, 2.09, 3.16, respectively ($p < 0.05$). After stratifying by Appalachian status, only triple negative cases had a statistically significant increased risk among Appalachian women. For non-Appalachian women, those with

Luminal B, HER2 enriched, and triple negatives subtypes had increased hazard of 1.69, 2.57, and 3.35, respectively ($p<0.05$) compared to Luminal A subtypes.

Subsequent primary

Among non-Appalachian residents, those women with Luminal B had a reduced risk of subsequent cancers (HR:0.76, 95% CI: 0.59,0.99).

V. DISCUSSION

The goal of the study was to examine the relationship between breast cancer HR/subtypes and the risk of recurrence and/or the risk of subsequent cancers among women in Kentucky. Additionally, the study investigated disparities in the mentioned-above outcomes between women living in Appalachian Kentucky compared to women living in non-Appalachian Kentucky. For the risk of recurrence outcome, the observed results were consistent with the current literature [16,39-42] and showed that women with Luminal A and B subtypes had a lower risk of recurrence compared to women with triple negative and HER2 enriched breast cancers. This is due to the fact that Luminal A and B cancerous cells are HR+ (their growth or proliferation is triggered by the presence of estrogen or progesterone). In order to control their growth and proliferation, patients often receive endocrine therapy to block the HR, thus metastasis can be controlled more effectively. The triple negative and HER2 enriched subtypes, on the other hand, tend to spread more aggressively and are unresponsive to hormone therapy. When cancerous breast cells spread to distant organs, they tend to re-emerge even after mastectomy or other treatment [39]. After a period of remission, cancerous cells that metastasized to distant regions and were not killed or controlled by treatment can proliferate again [46,47]. When we looked at HR status independently of HER2 status (2004-2016 analysis), it was also observed that ER+ and

PR+ subjects had a lower risk of recurrence than those positive to only one HR or those negative to both HR. Approximately 80% of breast cancers are ER+ and 65% of the ER+ tumors are also PR+ [48]. Because they are so prevalent, current endocrine treatment has been designed to target estrogen receptors primarily and progesterone secondarily to control the growth and proliferation of HR+ neoplastic cells. HR- (ER- and PR-) tumors grow and spread independently of the presence of estrogen or progesterone, as is the case with triple negative tumors, thus increasing the risk of recurrence.

ER+ only and Luminal B non-Appalachian subjects had reduced risk of subsequent cancers compared to non-Appalachian ER+ and PR+ and Luminal B subjects ($p<0.05$). One potential explanation of the reduced risk is that both respond to hormone therapy[49]. The majority of subsequent tumors among these women were breast cancer. ER+ and Luminal B women often receive endocrine therapy to treat their cancers. The treatment can have a protective effect against subsequent primaries that are also estrogen or HR+. The association between breast cancer subtypes and the risk of subsequent cancer needs to be further investigated.

Disparities between Appalachian and non-Appalachian women in the risk of recurrence and/or subsequent cancer can be partially explained by the inequity in access to quality healthcare and/or differences in cancer mortality rates between the two regions. Previous investigations suggest that Appalachian Kentuckians experience geographic isolation, a high prevalence of poverty, considerable barriers to healthcare (e.g., transportation, education ascertainment / literacy, social support, stigma), and later stages at diagnosis [20-22,45]. These regional disparities are a potential reason why breast cancer incidence rates are lower and mortality rates are higher

among Appalachia residents compared to non-residents. Also, non-Appalachian residents with breast cancer live longer or have a lower risk of death than Appalachian residents [20,22,23,45]. By living longer, they may live long enough to have subsequent cancers and/or recurrence. [50,51]

This research adds value to the epidemiology field by identifying which subtypes/HR status increases the risk of recurrence and subsequent cancer. In addition, the results of this investigation may potentially save lives by providing information that can be used in breast cancer education in Kentucky, assessing the sub-population at greater risk of recurrence and subsequent cancer (by subtypes), increasing screening in the sub-population at risk, and developing tailored interventions or communications messaging for each region.

This study had a number of limitations. The first limitation is that some subjects' demographic characteristics had "unknown" data. For example, 17.49% of the study sample had unknown tobacco use status, 50.30% of the women had unknown number of live births, 22.15% had unknown family history of the breast cancer, and 14.82% of subjects had unknown menopausal status. The "unknown" data potentially introduced non-differential bias and biased results toward the null. This can be observed in that some known risk factors such as family history or number of children had marginal or no statistically significant impact on the risk of the outcomes. Another potential limitation is the lack of data about occupations, socioeconomic status, comorbidities, and alcohol use. Not adjusting for these factors could have confounded or modified the results. The KCR dataset lacked information on Ki-67 protein, which may have

impacted the accuracy of the way breast cancer subtypes were defined. Lastly, the study did not adjust for the treatment receive by each subject. As mentioned earlier, cancer treatment in general and endocrine therapy in particular is often associated with lower risk of recurrence [46,47]. Not controlling for it could have confounded or modified the results.

In conclusion, breast cancer subtype/HR status is associated with the risk of subsequent primaries and recurrence. Also, there are disparities in the risk of recurrence between Appalachian and non-Appalachian women in Kentucky. Women in Appalachian KY had lower risk of recurrence than their non-Appalachian KY counterparts for similar subtypes adjusted for family history, menopausal status, age at diagnosis of the first primary, stage, tobacco use, and insurance status. Biologic differences may be responsible for differences seen in recurrence/subsequent primaries between Appalachian resident and non-Appalachian residents. A future direction of the study is a genome sequencing analysis of collected breast cancer tissues of Appalachian and non-Appalachian women to assess the potential biological or epigenetic differences between the two sub-populations that may explain the observed disparities in Kentucky

VI. ACKNOWLEDGEMENT

I would like to express my gratitude to Dr. Fleming for being the chair of my committee and for his help, guidance, and mentorship throughout the project. I want to thank Dr. Vanderpool for being on my committee and for her assistance in the editing of my capstone and providing insight into the cancer burden in Appalachian Kentucky. I would like to thank Dr. McDowell for being on my committee and for her guidance in approaching and understanding KCR data. I want to thank my Epidemiology classmates and professors for their support and encouragement throughout the capstone process. Lastly, I would to thank my friends and family for their support, prayers, and encouragement through all my years of education.

VII. REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre L, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca : a Cancer Journal for Clinicians.* 2018;68(6):394.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA: A Cancer Journal for Clinicians.* 2018;68(1):7-30.
3. Kamińska M, Ciszewski T, Łopacka-Szatan K, Miotła P, Starosławska E. Breast cancer risk factors. *Przeglad menopauzalny = Menopause review.* 2015;14(3):196.
4. Barnard ME, Boeke CE, Tamimi RM. Established breast cancer risk factors and risk of intrinsic tumor subtypes. *BBA - Reviews on Cancer.* 2015;1856(1):73-85.
5. Dumalaon J, Hutchinson A, Prichard I, Wilson C. WHAT CAUSES BREAST CANCER? A SYSTEMATIC REVIEW OF CAUSAL ATTRIBUTIONS AMONG BREAST CANCER SURVIVORS AND HOW THESE COMPARE TO EXPERT ENDORSED RISK FACTORS. *Asia-Pac J Clin Oncol.* 2014;10:157-157.
6. Opdahl S, Alsaker MDK, Janszky I, Romundstad PR, Vatten LJ. Joint effects of nulliparity and other breast cancer risk factors. *British Journal of Cancer.* 2011;105(5):731.
7. Kondov B, Milenkovikj Z, Kondov G, et al. Presentation of the molecular subtypes of breast cancer detected by immunohistochemistry in surgically treated patients. *Open Access Macedonian Journal of Medical Sciences.* 2018;6(6):961-967.
8. Badve S, Gökmen-Polar Y. *Molecular Pathology of Breast Cancer.* Cham : Springer International Publishing : Imprint: Springer; 2016.
9. Inic Z, Zegarac M, Inic M, et al. Difference between Luminal A and Luminal B Subtypes According to Ki-67, Tumor Size, and Progesterone Receptor Negativity Providing Prognostic Information. *Clinical Medicine Insights: Oncology.* 2014;8(2014).
10. Lee S, Koo J, Park B, et al. A difference of HER-2 amplification index between luminal B and HER2 enriched subgroup. *Cancer Res.* 2011;71(s8).
11. Aysola K, Desai A, Welch C, et al. Triple Negative Breast Cancer - An Overview. *Hereditary genetics : current research.* 2013;2013(Suppl 2).

12. Foulkes WD, Smith IE, Reis-Filho JS. Triple-Negative Breast Cancer. *The New England Journal of Medicine.* 2010;363(20):1938-1948.
13. Rusner C, Wolf K, Bandemer-Greulich U, et al. Risk of contralateral second primary breast cancer according to hormone receptor status in Germany. *Breast cancer research : BCR.* 2014;16(5):452-452.
14. Kurian AW, McClure LA, John EM, Horn-Ross PL, Ford JM, Clarke CA. Second Primary Breast Cancer Occurrence According to Hormone Receptor Status. *Journal of the National Cancer Institute.* 2009;101(15):1058-1065.
15. Ignatov A, Eggemann H, Burger E, Ignatov T. Patterns of breast cancer relapse in accordance to biological subtype. *Journal of Cancer Research and Clinical Oncology.* 2018;144(7):1347-1355.
16. Lee H, Park I, Cho H, Gwak G, Han S. Recurrence pattern of breast cancer according to the molecular subtype. *Breast.* 2015;24:S51-S51.
17. Idrovo AJ. Three criteria for ecological fallacy. *Environmental health perspectives.* 2011;119(8):A332.
18. Sedgwick P. The ecological fallacy. *BMJ.* 2011;343(jul27 1).
19. Yao N, Lengerich EJ, Hillemeier MM. Breast cancer mortality in Appalachia: reversing patterns of disparity over time. *Journal of health care for the poor and underserved.* 2012;23(2):715-725.
20. Yao N, Alcalá HE, Anderson R, Balkrishnan R. Cancer Disparities in Rural Appalachia: Incidence, Early Detection, and Survivorship. *Journal of Rural Health.* 2017;33(4):375-381.
21. Vanderpool RC, Huang B, Deng Y, et al. Cancer-Related Beliefs and Perceptions in Appalachia: Findings from 3 States. *The Journal of rural health : official journal of the American Rural Health Association and the National Rural Health Care Association.* 2019;35(2).
22. Smalls BL, Aroh A, McQuerry K, Adegboyega A, Schoenberg N, Hatcher J. Social support and breast cancer screening in rural Appalachia. *Psycho-Oncology.* 2018;27(9):2281-2288.

23. Huang B, Dignan M, Han D, Johnson O. Does Distance Matter? Distance to Mammography Facilities and Stage at Diagnosis of Breast Cancer in Kentucky. *Journal of Rural Health.* 2009;25(4):366-371.
24. Yang SC, Finlayson CA, Jacobs L, ClinicalKey. *Breast cancer.* 1st ed.. ed. Philadelphia: Philadelphia : Elsevier/Saunders; 2011.
25. lobular carcinoma. In: Oxford University Press; 2010.
26. McCart Reed AE, Kutasovic JR, Lakhani SR, Simpson PT. Invasive lobular carcinoma of the breast: morphology, biomarkers and 'omics. In: McCart Reed AE, ed. Vol 172015:12-12.
27. Virnig BA, Wang S-Y, Shamilyan T, Kane RL, Tuttle TM. Ductal Carcinoma In Situ: Risk Factors and Impact of Screening. *Journal of the National Cancer Institute Monographs.* 2010;2010(41):113-116.
28. Van Cleef A, Altintas S, Huizing M, Papadimitriou K, Van Dam P, Tjalma W. Current view on ductal carcinoma in situ and importance of the margin thresholds: A review. *Facts, views & vision in ObGyn.* 2014;6(4):210-218.
29. Sharma G, Dave R, Sanadya J, Sharma P, Sharma K. Various types and management of breast cancer: An overview. *Journal of Advanced Pharmaceutical Technology & Research.* 2010;1(2):109-126.
30. Rozhok AI, Degregori J. Toward an evolutionary model of cancer: Considering the mechanisms that govern the fate of somatic mutations. *Proceedings of the National Academy of Sciences of the United States of America.* 2015;112(29):8914-8921.
31. Hanahan D, Weinberg Robert a. Hallmarks of Cancer: The Next Generation. *Cell.* 2011;144(5):646-674.
32. Pietras K, Östman A. Hallmarks of cancer: Interactions with the tumor stroma. *Experimental Cell Research.* 2010;316(8):1324-1331.
33. Lee EYHP, Muller WJ. Oncogenes and tumor suppressor genes. *Cold Spring Harbor perspectives in biology.* 2010;2(10):a003236-a003236.
34. Hanahan D, Weinberg RA. The Hallmarks of Cancer. *Cell.* 2000;100(1):57-70.
35. Yersal O, Barutca S. Biological subtypes of breast cancer: Prognostic and therapeutic implications. *World journal of clinical oncology.* 2014;5(3):412-424.

36. Ades F, Zardavas D, Bozovic-Spasojevic I, et al. Luminal B breast cancer: molecular characterization, clinical management, and future perspectives. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2014;32(25):2794-2803.
37. Anderson K, Schwab R, Martinez M. Reproductive risk factors and breast cancer subtypes: a review of the literature. *Breast Cancer Research and Treatment.* 2014;144(1):1-10.
38. Warren JL, Yabroff KR. Challenges and Opportunities in Measuring Cancer Recurrence in the United States. *Journal Of The National Cancer Institute.* 2015;107(8).
39. Ahmad A. Pathways to Breast Cancer Recurrence. *ISRN Oncology.* 2013;2013.
40. Cossetti R, Tyldesley S, Speers C, Zheng Y, Gelmon K. Comparison of Breast Cancer Recurrence and Outcome Patterns Between Patients Treated From 1986 to 1992 and From 2004 to 2008. *J Clin Oncol.* 2015;33(1):65-U106.
41. Gerber B, Freund M, Reimer T. Recurrent Breast Cancer. *Deutsches Aerzteblatt Online.* 2010.
42. Shim HJ, Kim SH, Kang BJ, et al. Breast cancer recurrence according to molecular subtype. *Asian Pacific journal of cancer prevention : APJCP.* 2014;15(14):5539-5544.
43. Kim JY, Song HS. Metachronous double primary cancer after treatment of breast cancer. *Cancer research and treatment : official journal of Korean Cancer Association.* 2015;47(1):64.
44. Weir H, Johnson C, Thompson T. The effect of multiple primary rules on population-based cancer survival. *An International Journal of Studies of Cancer in Human Populations.* 2013;24(6):1231-1242.
45. Yao N, Lengerich E, Hillemeier M. Breast Cancer Mortality in Appalachia: Reversing Patterns of Disparity over Time. *Journal of Health Care for the Poor and Underserved.* 2012;23(2):715-725.
46. Schiavon G, Smith IE. Status of adjuvant endocrine therapy for breast cancer. In: Schiavon G, ed. Vol 162014:206-206.
47. Pan H, Gray R, Braybrooke J, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. *The New England Journal of Medicine.* 2017;377(19):1836-1846.

48. Kohler BA, Sherman RL, Howlader N, et al. Annual Report to the Nation on the Status of Cancer, 1975-2011, Featuring Incidence of Breast Cancer Subtypes by Race/Ethnicity, Poverty, and State. *Journal Of The National Cancer Institute.* 2015;107(6).
49. Gierach G, Curtis R, Pfeiffer RM, et al. Adjuvant endocrine therapy and risk of contralateral breast cancer among a cohort of US women with breast cancer. *Cancer Res.* 2016;76(s4).
50. Brown G. Living too long. *EMBO Rep.* 2015;16(2):137-141.
51. White MC, Holman DM, Boehm JE, Peipins LA, Grossman M, Jane Henley S. Age and Cancer Risk: A Potentially Modifiable Relationship: A Potentially Modifiable Relationship. *American Journal of Preventive Medicine.* 2014;46(3):S7-S15.

VIII. APPENDIX

Table 1. Descriptive statistics of the cohort of Kentucky women diagnosed with breast cancer between 2004-2016 and satisfied the inclusion criteria.

	Kentucky N= 31,058	**Appalachia N= 8,150**	**Non-Appalachia N= 22,908**	**p-value**
Age at diagnosis				
< 35	591 (1.90%)	156 (1.91%)	435 (1.90%)	
35 – 44	2,956 (9.52%)	751 (9.21%)	2,205 (9.63%)	
45 – 54	6,752 (21.74%)	1,690 (20.74%)	5,062 (22.10%)	**<0.0001**
55 – 64	8,489 (27.33%)	2,340 (28.71%)	6,149 (26.84%)	
65 – 74	7,061 (22.73%)	1,949 (23.91%)	5,112 (22.32%)	
75 – 84	4,001 (12.88%)	992 (12.17%)	3,009 (13.14%)	
85 +	1,208 (3.89%)	272 (3.34%)	936 (4.09%)	
Stage				
Localized	19,752 (63.60%)	4,961 (60.87%)	14,791 (64.57%)	
Regional	9,425 (30.35%)	6,808 (29.72%)	2,617 (29.72%)	**<0.0001**
Distant	1,731 (5.57%)	1,206 (5.26%)	525 (6.44%)	
Unknown	150 (0.49%)	47 (0.58%)	103 (0.45%)	
Subtypes				
ER+ Only	3,532 (11.37%)	975 (11.96 %)	2,557 (11.16%)	
PR+ Only	344 (1.11%)	99 (1.21 %)	245 (1.07%)	**0.0152**
ER+ and PR+	21,080 (67.87%)	5,418 (66.44%)	15,662 (68.37%)	
ER- and PR-	6,102 (19.65 %)	1,658(20.34%)	4,444 (19.40%)	
Race				
Black	2,126 (6.85%)	115 (1.41%)	2,011 (8.78%)	
White	28,664 (92.29%)	7,993 (98.07%)	20,671 (90.23%)	**<0.0001**
Other	182 (0.59%)	11 (0.13%)	171 (0.75%)	
Unknown	86 (0.28%)	31 (0.38%)	55 (0.24%)	
Tobacco user				
No	15,107 (48.64%)	3,876 (47.56%)	11,231 (49.03%)	

Yes	11,141 (35.87%)	2,718 (33.35%)	8,423 (36.77%)	**<0.0001**
Unknown	4,810 (15.49 %)	1,556 (19.09%)	3,254 (14.20%)	
Family History				
Yes	10,419 (33.55%)	2,545 (31.23%)	7,874 (34.37%)	
No	14,487 (46.65%)	3,439 (42.20%)	11,048 (48.23%)	**<0.0001**
Unknown	6,152 (19.81%)	2,166 (26.57%)	3,986 (17.40%)	
Menopausal Status				
Pre	6,482 (20.87 %)	1,729 (21.21%)	4,753 (20.75%)	
Post	19,866 (63.96%)	4,969 (60.97%)	14,897 (65.03%)	**<0.0001**
Unknown	4,710 (15.17%)	1,452 (17.82%)	3,258 (14.22%)	
Insurance				
Not Insured	687 (2.21%)	229 (2.81%)	458 (2.00%)	
Insured	14,933 (48.08%)	3,241 (39.77%)	11,692 (51.04%)	
Medicaid	2,598 (8.37%)	1,065 (13.07%)	1,533 (6.69%)	**<0.0001**
Medicare	12,585 (40.52 %)	3,505 (43.01%)	9,080 (39.64%)	
Unknown	255 (0.82%)	110 (0.63%)	145 (0.63%)	

- Follow-up period 5 years maximum
- Bold: Statistically significant ($p < 0.05$)

Table 2. Outcomes after 60 months follow-up (maximum) of the analytic cohort of subjects diagnosed with breast cancer between 2004 and 2016 in Kentucky.

	Kentucky N= 31,058	**Appalachia N= 8,150**	**Non-Appalachia N= 22,908**	**p-value**
Recurrence				
No	29,045 (93.71%)	7,640 (93.74%)	21,405 (93.44%)	0.34
Yes	2,013 (6.48%)	510 (6.26%)	1,503 (6.56%)	
Multiple primaries				
No	28,566 (91.98%)	7,504 (92.07%)	21,062 (91.94%)	0.71
Yes	2,492 (8.02%)	646 (7.93%)	1,846 (8.06%)	

Table 3. Five most frequent second primary cancers among women in the breast cancer cohort (2004-2016).

Kentucky N= 2,492		**Appalachia N= 646**		**Non-Appalachia N= 1,846**	
Breast	1,290 (51.77%)	Breast	294 (45.51%)	Breast	996 (53.95%)
Lung and Bronchus	291 (11.68%)	Lung and Bronchus	93 (14.40%)	Lung and Bronchus	198 (10.73%)
Melanoma and skin	77 (3.09%)	Thyroid	26 (4.02%)	Melanoma and skin	61 (3.30%)
Corpus Uteri	76 (3.05%)	Corpus Uteri	21 (3.25%)	Kidney and renal pelvis	57 (3.09%)
Kidney and renal pelvis	71 (2.81%)	Melanoma and skin	16 (2.48%)	Corpus Uteri	55 (2.98%)

Table 4. Risk of multiple primaries and recurrence 2004-2016 (Univariate analysis) among women in the breast cancer cohort.

	Multiple Primaries			**Recurrence**		
	Kentucky	**Appalachia**	**Non-Appalachia**	**Kentucky**	**Appalachia**	**Non-Appalachia**
	HR (95% CI)	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***
Subtypes						
ER+ and PR+	**Ref**	Ref	Ref	Ref	Ref	Ref **1.95 (1.68, 2.27)**
ER+ Only	0.88 (0.77,1.00)	1.01 (0.79, 1.28)	**0.83 (0.75,0.96)**	**1.83 (1.60, 2.08)**	**1.52 (1.17, 1.97)**	**2.61 (1.75, 3.89)**
PR+ Only	0.97 (0.66, 1.43)	1.61 (0.89,2.93)	0.76 (0.46, 1.26)	**2.61 (1.86, 3.65)**	**2.59 (1.39, 4.87)**	**2.85 (2.55, 3.19)**
ER- and PR-	**0.88 (0.79, 0.97)**	0.96 (0.78, 1.17)	**0.85 (0.75, 0.96)**	**2.70 (2.45, 2.97)**	**2.29 (1.88, 2.78)**	
Stage						
Localized	Ref	Ref	Ref	Ref	Ref	Ref
Regional	1.07 (0.98, 1.16)	1.02 (0.86, 1.21)	1.08 (0.98, 1.20)	**3.12 (2.85, 3.42)**	**2.54 (2.12, 3.03)**	**3.35 (3.02, 3.72)**
Distant	**1.43 (1.20, 1.70)**	**1.43 (1.04, 1.98)**	**1.42 (1.15,1.76)**	**1.91 (1.48, 2.47)**	1.60 (0.99, 2.59)	**2.05 (1.52, 2.77)**
Unknown	1.13 (0.60, 2.10)	0.73 (0.18, 2.94)	1.30 (0.65, 2.60)	1.15 (0.43, 3.06)	1.74 (0.43, 6.98)	0.85 (0.21, 3.41)
Family History						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	**1.01 (1.004, 1.20)**	0.99 (0.83,1.20)	**1.13 (1.02,1.25)**	0.95 (0.86, 1.04)	1.09 (0.88, 1.33)	0.91 (0.81, 1.02)
Unknown	1.03 (0.93, 1.15)	0.92 (0.76,1.12)	1.08 (0.95,1.22)	**0.80 (0.71, 0.91)**	0.92 (0.74, 1.15)	**0.75 (0.65, 0.88)**
Menopausal Status						
Pre	Ref	Ref	Ref	Ref	Ref	Ref

Post	**1.61 (1.44, 1.79)**	**1.55 (1.25, 1.91)**	**1.63 (1.44,1.86)**	**0.74 (0.67, 0.82)**	**0.71 (0.58, 0.86)**	**0.75 (0.67, 0.84)**
Unknown	**1.26 (1.09, 1.46)**	**1.26 (0.96, 1.66)**	**1.26 (1.05, 1.50)**	**0.71 (0.61, 0.82)**	**0.69 (0.52, 0.91)**	**0.71 (0.60, 0.85)**
Age at diagnosis						
< 35	Ref	Ref	Ref	Ref	Ref	Ref
35 – 44	0.94 (0.63, 1.41)	0.49 (0.23, 1.02)	1.18 (0.72, 1.95)	**0.64 (0.51, 0.82)**	0.67 (0.42, 1.08)	**0.63 (0.48, 0.83)**
45 – 54	1.31 (0.89, 1.92)	1.13 (0.59, 2.15)	1.42 (0.88, 2.28)	**0.44 (0.35, 0.55)**	**0.50 (0.32, 0.79)**	**0.42 (0.32, 0.55)**
55 – 64	**1.63 (1.11, 2.37)**	1.20 (0.64, 2.79)	**1.86 (1.16, 2,98)**	**0.41 (0.32, 0.51)**	**0.45 (0.29, 0.70)**	**0.39 (0.30, 0.51)**
65 – 74	**2.26 (1.55, 3.30)**	1.76 (0.94, 3.34)	**2.54 (1.59, 4.06)**	**0.31 (0.24, 0.39)**	**0.34 (0.22, 0.55)**	**0.30 (0.23, 0.39)**
75 – 84	**2.44 (1.67, 3.58)**	1.68 (0.88, 3.23)	**2,86 (1.78, 4.59)**	**0.37 (0.29, 0.48)**	**0.38 (0.23, 0.65)**	**0.37 (0.27, 0.49)**
85 +	**2.31 (1.31, 3.38)**	1.12 (0.50, 2.49)	**2.89 (1.74, 4.79)**	**0.46 (0.33, 0.64)**	**0.25 (0.10, 0.61)**	**0.50 (0.35, 0.72)**
Tobacco user						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1**.41 (1.30, 1.54)**	**1.44 (1.22, 1.71)**	**1.41 (1.27, 1.55)**	1.04 (0.94, 1.15)	1.13 (0.93, 1.38)	1.01 (0.90, 1.13)
Unknown	1.10 (0.98, 1.24)	0.91 (0.72, 1.14)	**1.20 (1.04, 1.37)**	**1.17 (1.04, 1.15)**	1.07 (0.85, 1.36)	**1.22 (1.06, 1.42)**
Insurance						
Insured	Ref	Ref	Ref	Ref	Ref	Ref
Not Insured	1.21 (0.91, 1.60)	1.21 (0.73, 1.98)	1.22 (0.87, 1.72)	1.29 (0.98, 1.68)	1.35 (0.87, 2.12)	1.40 (0.98, 1.99)
Medicaid	**1.43 (1.23, 1.66)**	**1.46 (1.13, 1.88)**	**1.44 (1.20, 1.74)**	**1.56 (1.34, 1.80)**	**1.66 (1.31, 2.11)**	**1.54 (1.28, 1.84)**
Medicare	**1.73 (1.59, 1.88)**	**1.81 (1.52, 2.16)**	**1.71 (1.57, 1.89)**	0.91 (0.83,1.01)	0.92 (0.75, 1.13)	0.91 (0.82, 1.02)
Unknown	**1.77 (1.17, 2.66)**	**2.01 (1.12, 3.61)**	1.61 (0.89, 2.93)	1.06 (0.61 ,1.84)	1.14 (0.54, 2.42)	1.03 (0.46, 2.29)

- Bold: Statistically significant ($p < 0.05$)
- HR: Hazard ratio

Table 5. Multivariable logistic regression analysis for predicting association between breast cancer subtypes and the outcomes 2004-2016. Adjusted for family history, menopausal status, age at diagnosis, stage, tobacco use, and insurance status.

	Multiple Primaries			**Recurrence**		
	Kentucky	**Appalachia**	**Non-Appalachia**	**Kentucky**	**Appalachia**	**Non-Appalachia**
	HR (95% CI)	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***
Subtypes						
ER+ and PR+	**Ref**	Ref	Ref	Ref	Ref	Ref
ER+ Only	**0.85 (0.74, 0.96)**	0.98 (0.77,1.25)	**0.80 (0.69, 0.94)**	**1.75 (1.53, 1.99)**	**1.49 (1.15, 1.95)**	**1.84 (1.58, 2.14)**
PR+ Only	1.05 (0.71, 1.54)	1.71 (0.94, 3.12)	0.82 (0.49, 1.36)	**2.38 (1.69, 3.33)**	**2.47 (1.31, 4.66)**	**2.30 (1.54, 3.43)**
ER- and PR-	0.94 (0.84, 1.04)	1.03 (0.84, 1.26)	0.91 (0.80, 1.03)	**2.44 (2.21, 2.69)**	**2.07 (1.99, 3.13)**	**2.58 (2.31, 2.89)**

- Bold: Statistically significant

Table 6. Distribution of the exposure of interest among women in the breast cancer cohort (2011-2016).

	Kentucky N= 15,371	**Appalachia N= 3,997**	**Non-Appalachia N= 11,374**	**p-value**
Subtypes				
Luminal A	10,554 (68.66%)	2,643 (66.12%)	7,911 (69.55%)	
Luminal B	1,574 (10.24 %)	429 (10.73%)	1,145 (10.07%)	**0.0014**
HER2 enriched	719 (4.68%)	207 (5.18%)	512 (4.50%)	
Triple Negative	1,826 (11.88%)	512 (12.81%)	1,314 (11.55%)	
Other	698 (4.54%)	206 (5.15%)	492 (4.33%)	

- Luminal A: ER+ and/or PR +, HER2-
- Luminal B: ER+ and/or PR +, HER2+
- HER2 enriched: ER-, PR-, HER2+
- Triple negative: ER-, PR-, HER2-
- Other: Borderline result, one or more test(s) not performed, not documented

Table 7. Multivariable logistic regression analysis for predicting association between breast cancer subtypes and the outcomes 2011-2016. Adjusted for family history, menopausal status, age at diagnosis, stage, tobacco use, and insurance status.

	Multiple Primaries			**Recurrence**		
	Kentucky (Overall)	**Appalachia**	**Non-Appalachia**	**Kentucky (Overall)**	**Appalachia**	**Non-Appalachia**
	HR (95% CI)	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***	***HR (95% CI)***
Subtypes						
Luminal A	Ref	Ref	Ref	Ref	Ref	Ref
Luminal B	0.82 (0.66, 1.02)	0.97 (0.65, 1.43)	**0.76 (0.59,0.99)**	**1.61 (1.28,2.03)**	1.42 (0.89, 2.29)	**1.69 (1.29, 2.20)**
HER2 enriched	0.87 (0.64, 1.18)	1.09 (0.65, 1.86)	0.77 (0.45, 1.31)	**2.09 (1.57, 2.80)**	1.03 (0.49, 2.15)	**2.57 (1.87, 3.53)**
Triple Negative	0.85 (0.70,1.04)	0.94 (0.68, 1.40)	0.81 (0.64, 1.03)	**3.16 (2.64, 3.79)**	**2.76 (1.91, 3.98)**	**3.35 (2.72, 4.13)**
Other	**1.29 (1.01,1.65)**	1.13 (0.69, 1.84)	**1.37 (1.02, 1.83)**	0.99 (0.63, 1.530	1.21 (0.58, 2.51)	0.88 (0.50, 1,54)

- Bold: Statistically significant
- Luminal A: ER+ and/or PR +, HER2-
- Luminal B: ER+ and/or PR +, HER2+
- HER2 enriched: ER-, PR-, HER2+
- Triple negative: ER-, PR-, HER2-
- Other: Borderline result, one or more test(s) not performed, not documented

Figure 1.

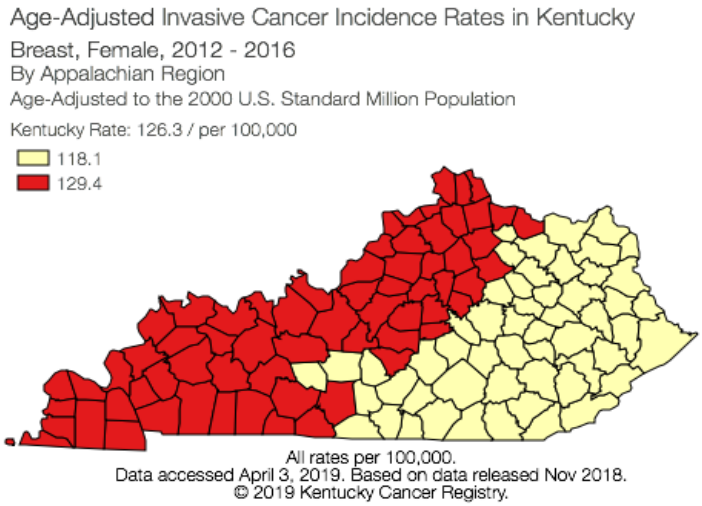


Figure 2.

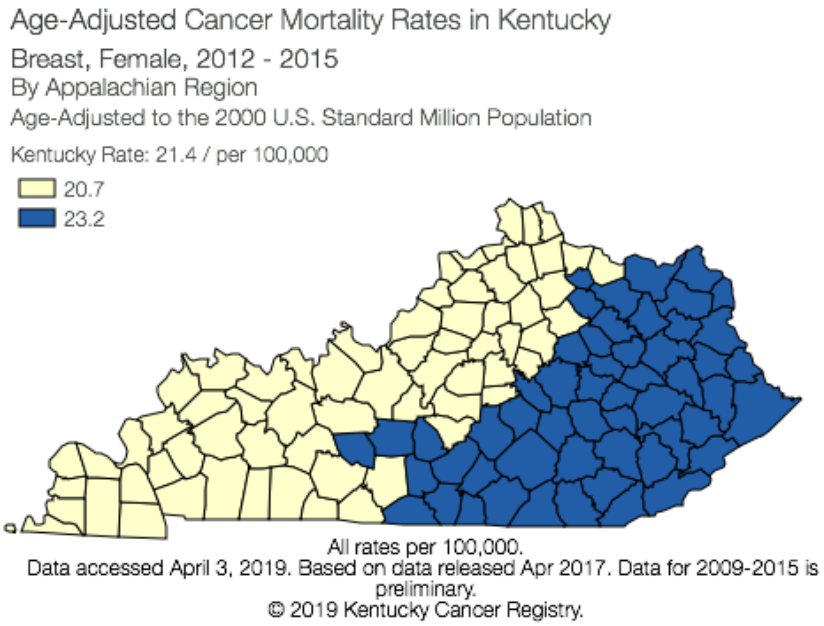


Figure 3

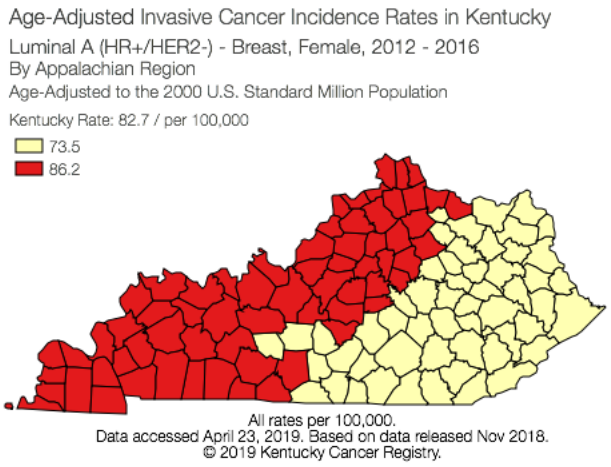


Figure 4

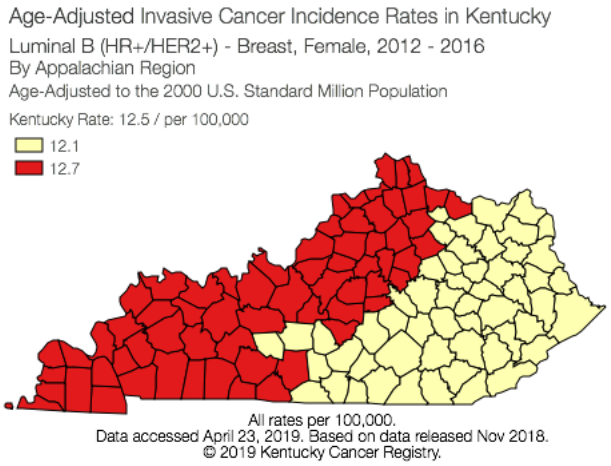


Figure 5.

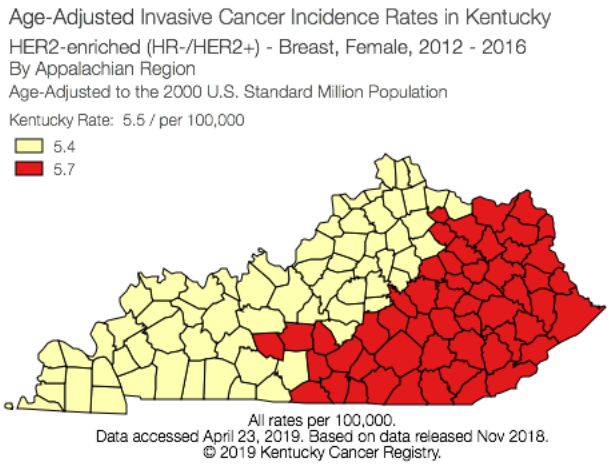
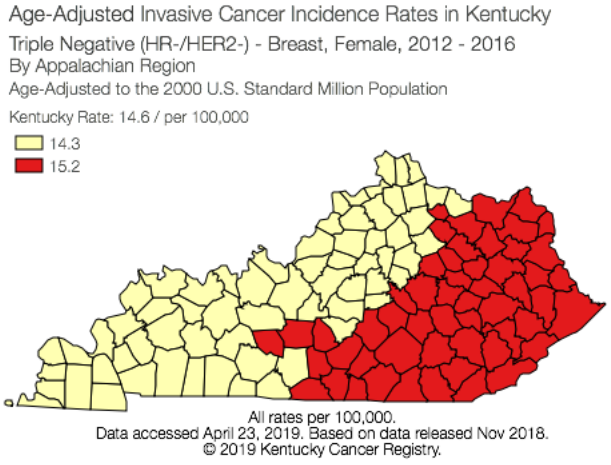


Figure 6



IX. BIOGRAPHICAL SKETCH

Pierre Fwelo was born and raised in Kinshasa, Democratic Republic of Congo and moved to Lexington, KY in 2011. He attended the University of Kentucky where he majored in Biology and earned a Bachelor of Science degree in 2016. From 2016 – 2017 he served as a research learner/lab technician at the Delisle Lab, Department of Physiology, College of Medicine at the University of Kentucky. He is currently a candidate for a Master of Public Health degree with a concentration in Epidemiology at the University of Kentucky College of Public Health.