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Time to Diagnosis of Second Primary Cancers among Patients with Breast Cancer

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Abstract

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Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Many breast cancer diagnoses and second cancers are associated with *BRCA* gene mutations. Early detection of cancer is necessary to improve health outcomes, particularly with second cancers. Little is known about the influence of risk factors on time to diagnosis of second primary cancers after diagnosis with *BRCA*-related breast cancer. The purpose of this cohort study was to examine the risk of diagnosis of second primary cancers among women diagnosed with breast cancer after adjusting for *BRCA* status, age, and ethnicity. The study was guided by the empirical evidence supporting the mechanism of action in the mutation of *BRCA* leading to the development of cancer. Composite endpoint was used to define second primary cancer occurrences, and Kaplan-Meier survival curves were used to compare the median time-to-event among comparison groups and *BRCA* gene mutation status. Cox proportional hazards was used to examine the relationships between age at diagnosis, ethnicity, *BRCA* gene mutation status, and diagnosis of a second primary cancer. The overall median time to event for diagnosis of second primary cancers was 14 years. The hazard ratios for *BRCA2* = 1.47, 95% CI [1.03 – 2.11], White = 1.511, 95% CI [1.18 – 1.94], and American Indian/Hawaiian = 1.424, 95% CI [1.12 – 1.81] showed positive significant associations between *BRCA*2 mutation status and risk of diagnosis of second primary colorectal, endometrial, cervical, kidney, thyroid, and bladder cancers. Data on risk factors for development of second cancers would allow for identification of appropriate and timely screening procedures, determining the best course of action for prevention and treatment, and improving quality of life among breast cancer survivors.

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Dedication

This dissertation is dedicated to God the Father, God the Son, and God the Holy Ghost. The LORD has been my inspiration and strength in this study. By my own strength, I could not have prevailed. His grace and comfort are like new every morning. Great is His faithfulness! To Him be all the glory, dominion, adoration, and praise for ever and ever. Amen.

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Finally, I would like to thank other family members, friends, and colleagues who stood by me giving me positive reinforcement and encouragement throughout this dissertation process.

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Chapter 1: Introduction to the Study

Breast cancer is a heterogeneous disease with multiple clinical presentations and tumor-specific features (Singletary, Robb, & Hortobagyi, 2004). Genetic mutations are implicated in breast cancer development and prognosis, as well as in the development of other types of cancers. Genetics are implicated in both sporadic and familial breast cancers (Nussbaum, McInnes, & Willard, 2007). Genes associated with triggering the process of cancer formation include those involved in encoding certain proteins responsible for cell proliferation in the signaling pathway, cytoskeletal components responsible for maintaining contact inhibition, the mitotic cycle regulators, components of apoptotic (cell death) machinery, and mutation detecting and repairing proteins (Nussbaum et al., 2007).

Genetic mutations can trigger a gain-of-function in one allele of a proto-oncogene (Le, Bhushan, & Tolles, 2011), while other mutations may trigger a loss of function of both alleles or a dominant negative mutation of one allele of a tumor-suppressor gene (Nussbaum et al., 2007). *BRCA1* and *BRCA2* are known tumor suppressor genes (Venkitaraman, 2002). Genetic mutations are also involved in chromosomal translocations that give rise to misexpression of genes or create chimeric genes encoding proteins that have acquired new functional properties (Nussbaum et al., 2007). Once a gene mutation is initiated, cancer progresses by accumulating additional genetic destruction. This progression occurs through mutations or epigenetic silencing of the

genes that encode the cellular machinery that repairs damaged DNA and maintains cytogenetic integrity (Nussbaum et al., 2007).

BRCA1 and BRCA2 mutations are associated with multiple primary cancers. There are limited data on the risk factors of BRCA1/BRCA2 gene mutations and time to diagnosis of second cancers after initial diagnosis with breast cancer in the United States. In addition, the roles of gender, ethnicity, and age in the time to development of second cancers have not been well defined. I examined the time to diagnosis of colorectal, endometrial, cervical, kidney, thyroid, and bladder cancers before and after stratification by, ethnicity, and age in a breast cancer population with BRCA mutations.

Background

BRCA1 and BRCA2 are known tumor suppressor genes (Venkitaraman, 2002). Deficiencies of BRCA1 (including protein loss expression, promoter hypermethylation, and gene copy deletion) have been implicated in the BRCA1 down-regulation that is directly related to breast tumor initiation, progression, and treatment (Ren et al., 2013). In most breast and ovarian cancers that have been investigated among BRCA mutation carriers, deletion of the normal allele gave rise to a loss of function, leading to the classification of BRCA1 and BRCA2 as tumor suppressor genes.

BRCA1 and BRCA2 are used in multiple functions within cells, including homologous DNA repair, genomic stability, transcriptional regulation, protein ubiquitination, chromatin remodeling, and cell cycle control (Venkitaraman, 2002).

From a treatment perspective, BRCA1 expression level acts as a determinant of response to different classes of chemotherapy (Mullan, Gorski, & Harkin, 2006). Tumor cells without BRCA1 are usually hypersensitive to DNA damaging chemotherapeutic agents (e.g., mitomycin C and cisplatin) (Fedier et al., 2003). BRCA1 deficiency is an important therapeutic target, and the reactivation of BRCA1 by secondary mutations has been demonstrated to give rise to therapy resistance (Drost & Jonkers, 2014).

Statement of the Problem

BRCA gene mutation related to breast cancer has been reported in both male and female genders (Al-Mulla et al., 2009; Liede, Karla, & Narod, 2004). BRCA gene mutations have been reported to have an increased risk of developing second primary cancers (Le et al., 2008). One out of every four hereditary breast cancer diagnoses (Easton, 1999) and about 5-10% of all breast cancer diagnoses (Campeau, Foulkes, & Tischkowitz, 2008) are associated with BRCA1/BRCA2 gene mutations. There is also evidence of an increased risk of developing other cancers among individuals with BRCA gene mutations (Al-Mulla et al., 2009). While not all breast cancers are caused by BRCA gene mutations, it has been observed that those that are caused by the BRCA gene mutations may be sporadic and occur before 50 years of age (Al-Mulla et al. 2009).

Scholars suggested a strong association between BRCA1/BRCA2 gene mutations and endometrial (Oh, Kim, Kim, & Kim, 2015), cervical (Rheim, Fisher, Bosse, Wappenschmidt, & Schmutzler, 2007), ovarian (Evans et al., 2009), prostate (Agalliu et al., 2007), bladder (Neveling et al., 2007), gallbladder (The Breast Cancer Linkage

Consortium, 1999), stomach (Bermejo & Hemminki, 2004), malignant melanoma (The Breast Cancer Linkage Consortium, 1999), uterus (Thomson, Easton, & the Breast Cancer Linkage Consortium, 2002), colon (Kadouri et al., 2007; Niell et al., 2004), and pancreatic cancers (Lubezky et al., 2012) cancers.

There are limited data on the risk factors of BRCA1/BRCA2 gene mutations and time to diagnosis of second cancers after breast cancer diagnosis among varying age, gender, and racial and ethnic groups in the United States. The role of age and ethnicity in the diagnosis of BRCA-related cancers has been investigated, but needs further clarification. In this study, I addressed the gap in the literature by examining these variables. I intended to include males because both genders are at risk from BRCA-related cancer (Al-Mulla et al., 2009; Giordano, Cohen, Buzdor, Perkins, & Hortobagyi, 2004; Jemals et al., 2003; Liede et al., 2004); however, only female gender were observed in the dataset. Additionally, there is a reported correlation with a younger age of diagnosis of cancer (Bermejo & Hemminki, 2004; Lee et al., 2008; Papelard et al., 2000) and a high mortality rate for pancreatic and colon cancers (Leet al., 2011). The initial intent was to analyze only pancreatic and colon cancer. Because insufficient data for power were obtainable in the BCFR dataset when variables were limited to pancreatic and colorectal cancer, the study was expanded to include endometrial, cervical, kidney, thyroid, and bladder cancer. This enabled me to achieve a study power of 80% or greater using the composite endpoint technique. In this study, I explored ethnicity and age-specific risk factors and their respective associations to time to event, defined as

diagnosis of colorectal, endometrial, cervical, kidney, thyroid, or bladder cancer, among patients with an initial diagnosis of BRCA1/BRCA2 breast cancer.

Purpose of the Study

The purpose of this quantitative study was to analyze the association of gender, ethnicity, and age of diagnosis of breast cancer with time to diagnosis for second primary cancers among subjects diagnosed with breast cancer. Specifically, I investigated the associations of exposures to outcomes within the framework of time-to-event analysis.

Research Questions and Hypotheses

The aim of the study was to answer the following questions and test the associated hypotheses:

RQ1: Is there a relationship between BRCA mutation status and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among women with breast cancer?

H_{01}: There is no relationship between BRCA mutation status and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among women with breast cancer.

H_{a1}: There is a relationship between BRCA mutation status and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among women with breast cancer.

RQ2: Is there a relationship between ethnicity and age status and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among women with BRCA-related breast cancer?

H_{02}: There is no relationship between ethnicity and age status and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among women with BRCA-related breast cancer.

H_{A2}: There is a relationship between ethnicity and age status and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among women with BRCA-related breast cancer.

RQ2a: Is there a relationship between ethnicity and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among women with BRCA-related breast cancer?

RQ2b: Is there a relationship between age status and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among women BRCA-related breast cancer?

RQ3: Is there a relationship between gender and time to diagnosis of second cancers, pancreatic, colorectal, endometrial, or cervical, among men and women diagnosed with BRCA-related breast cancer?

H_{03}: There is no relationship between gender and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among men and women diagnosed with BRCA-related breast cancer.

H_{a3}: There is a relationship between gender and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among men and women diagnosed with BRCA-related breast cancer.

In each case, differences in median time distributions were examined using the Kaplan-Meier survival curves and tested using the log-rank test.

Conceptual Framework

The conceptual framework I used for this study was based on genetic fundamental principles and published empirical data that support a mechanism of action for BRCA in breast and other cancers. In 1990, the King laboratory localized the BRCA1 gene to chromosome 17q (Hall et al., 1990). Later, the BRCA2 gene was localized to chromosome 13q12-13 (Wooster et al., 1994). BRCA1 and BRCA2 are tumor suppressor genes, for which many different mutations have been identified (Petrucelli et al., 2011). Significant gene rearrangements and missense mutations (changes in amino acids sequence) give rise to mutant phenotypes (Meindl, 2002). Repeated episodes of DNA damage may occur after exposure to stressors, such as reactive oxygen species, cytotoxic chemotherapy, and ionizing radiation, triggering the mechanism of carcinogenesis (Bougie & Weberpals, 2011).

These mutations may be specific to certain populations and ethnicities (Bougie & Weberpals, 2011). John et al. (2011) found that, among African Americans, 25% of *BRCA*1 mutations were frameshift, 38% were missense, 13% were nonsense, and 25% were splice mutations; differing percentages were found in other ethnic groups. Non-

Hispanic White patients were found to show 36% frameshift, 14% missense, 29% nonsense, and 21% splice for BRCA1 mutations (John et al., 2011). Among the Ashkenazi Jewish population, three BRCA mutation types, including BRCA1 185delAG, BRCA1 5382insC, and BRCA*2* 6174delT have been well-documented (Moslehi et al., 2000). Individuals with a positive diagnosis of BRCA gene mutations have been reported to be more susceptible to second malignancies, but the underlying mechanisms have not been fully elucidated (Bougie & Welberpals, 2011). Empirical data on the known mechanisms of tumor suppressor gene-related carcinogenesis and the published differing impacts of BRCA mutations on both genders, as well as various ethnicities provided the framework for the choice of variables and the research questions, were used in this study.

Nature of the Study

This study was a quantitative cohort design using secondary data. In cohort studies, sequences, patterns of change, growth, or trends over time are examined (Houser, 2012). By describing the characteristics of groups of people at certain time periods, investigators attempt to identify risk factors for particular diseases and health conditions (Houser, 2012). I intended to use three cohorts to answer my research questions, but the design was changed to two cohorts because no male subjects were included in the study. Question 3 was intended to examine gender and relationship with second primary cancers. The first cohort consisted of women with and without a diagnosis of BRCA-related breast cancer and a subsequent diagnosis of pancreatic, colorectal, endometrial, or cervical cancer. I compared time to diagnosis of colorectal, endometrial, cervical cancer,

kidney, thyroid, or bladder, among those women based on their BRCA status. The second cohort was women with a diagnosis of BRCA-related breast cancer. I analyzed the relationship of the three risk factors, BRCA status, age at initial diagnosis of breast cancer and ethnicity, to time to diagnosis of colorectal, endometrial, cervical, kidney, thyroid, and bladder cancer. The third cohort was intended to include men and women with a diagnosis of BRCA-related breast cancer, for whom I would compare time to diagnosis of colorectal, endometrial, cervical, kidney, thyroid, and bladder cancer based on gender. As noted previously, this cohort was not used. In the analysis of all research questions, the dependent variable was time to diagnosis of second primary cancers, specifically, colorectal, endometrial cervical, kidney, thyroid, and bladder. The independent variables were unique for each question and included the presence of BRCA mutation, ethnicity, and age. I assessed the statistical significance of the relationship between dependent and independent variables using Cox proportional hazards (CPH).

Operational Definitions

BRCA1: BRCA1 is a tumor suppressor gene on chromosome 17 that functions by helping to suppress cell growth. Some mutations in the BRCA1 gene are correlated with a higher risk of breast, ovarian, prostate, and other types of cancer (National Cancer Institute [NCI], 2014). For the purpose of this study, BRCA1 mutation diagnosis is retrievable from the dataset and is dichotomous.

BRCA2: BRCA2 is a tumor suppressor gene on chromosome 13 that functions by helping to suppress cell growth. Certain mutations in the BRCA2 gene are associated

with higher risk of breast, ovarian, prostate, and other types of cancer (NCI, 2014). For the purpose of this study, BRCA2 mutation diagnosis is retrievable from the dataset and is dichotomous.

BRCA both 1 and 2: BRCA both 1 and 2 refers to individuals diagnosed with both BRCA1 and BRCA2 gene mutations. BRCA both 1 and 2 is retrievable from the dataset and is dichotomous.

Second cancers: For the purpose of this study, second cancer refers to any cancer that a patient experienced after initial diagnosis with BRCA1- or BRCA2-related breast cancer. Specifically, this study included pancreatic, colon, endometrial, and cervical cancer.

Time to event: Time to event in this study was the time it takes for a patient with a BRCA1 or BRCA2 mutation related to breast cancer to be diagnosed with another form of cancer. Specifically, this study included only diagnosis with colorectal, endometrial, cervical, kidney, thyroid, or bladder cancer after diagnosis of breast cancer.

Assumptions, Limitations, and Scope of the Study

The source of the sample population in a secondary data analysis may lead to bias in the study. The sample population was drawn from the Breast Cancer Family Registries (BCFR), which contained clinical and population data on BRCA cancer-related incidence and time to diagnosis of a second primary cancer (NCI, 2014). The study was limited to the data available in the dataset. One limitation of this study was the nonavailability of data from all 50 states' cancer registry in the BCFR databases. Another potential

limitation was related to the size of the dataset. The available data were limited due to rare screening of the disease and data availability. The ability of distinguishing secondary from second primary cancers in the data set did not pose a limitation. This study was originally intended to involve only pancreatic and colorectal cancer, unless there was an insufficient sample size. Finally, analyses of relationships among variables were limited by what information was collected originally. It was not possible for me to gain additional information about the subjects in the cohorts. An assumption was that the dataset contained correct diagnoses of BRCA mutations, cancers, age, gender, and ethnicity. It was also assumed that the BCFR dataset population was representative of the population, but results may not be generalizable to other populations.

Significance of the Research

Breast cancer is the most common cancer among women and the second most common cause of cancer-related death among women (NCI, 2013). The ratio of mortality to incidence is highest in developing countries (Groot et al., 2006). The 10-year period total cost of introducing Stage I treatment was estimated by Groot et al. (2006) to be $ 68 million in Africa, $143 million in Asia, and $3,879 million in North America. Treatment of early stage cancer patients is more effective than treatment in the later stages, supporting the need to continually strive for better and more effective means of early detection.

Those who carry BRCA mutations are also at risk of other types of cancer beyond breast cancer. I initially selected time to development of pancreatic and colon cancer in

patients with breast cancer and BRCA gene mutations as variables in this study because pancreatic and colon cancers are known to be associated with BRCA mutations and because of the relatively poor prognoses of these cancers (Al-Mulla et al., 2009; Kadouri et al., 2007; Le et al., 2011). Pancreatic adenocarcinoma is aggressive and is usually already metastasized at presentation; frequently patients have a prognosis of 6 months or less for survival time (Le et al., 2011). Colon cancer is the third most common and third most deadly cancer in the United States (Le et al., 2011), and BRCA gene mutations may be associated with early onset of colon cancer (Suchy et al., 2010). Endometrial and cervical cancer were added to the variables in order to have sufficient data to analyze, and because these cancers have also been associated with BRCA mutations. Endometrial cancer is the most common cancer of the female reproductive system, accounting for 6% of all the cancers among women in the United States (NCI, 2014). The association between germline mutations in BRCA genes and the risk of endometrial cancer remains unclear, but several case reports of endometrial carcinoma in women with a BRCA mutation exist (Oh, Kim, Kim, & Kim, 2015; Levine et al., 2001). In recent years, cervical cancer has become a growing concern in public health in the United States. According to the Surveillance, Epidemiology, and End Results Program (SEER, 2015), the number of new cases of cervix uteri cancer was 7.7 per 100,000 women per year. The number of deaths was 2.3 per 100,000 women per year (author, year). These rates are age-adjusted and based on 2008-2012 cases and deaths (author, year).

There remains a gap in the literature regarding gender, ethnicity, and age of diagnosis as risk factors for the development of a second primary cancer in a BRCA positive, breast cancer population. To date, scholars have analyzed time to diagnosis of a second primary colon cancer in a BRCA positive, breast cancer population, and few researchers have investigated the time to diagnosis of a second primary pancreatic cancer in a population with BRCA-related breast cancer (Brose et al., 2002; Mocci et al., 2013). Mocci et al. (2013) did not analyze different ethnic groups or time to event of the pancreatic cancer. Other scholars have explored the risk for developing second primary cancers. Brose et al. (2002) estimated BRCA1-related cancer risks for individuals ascertained in a breast cancer risk evaluation clinic and that found by age 70, female breast cancer risk was 72.8%, the risk for developing a second primary breast cancer by age 70 was 40.5%, a two-fold increased risk of colon cancer, threefold risk of pancreatic cancer, fourfold risk of stomach cancer, and 120-fold increased risk of fallopian tube cancer among BRCA1 mutation carriers with breast cancer (Brose et al., 2003). An increased risk for developing a second primary cancer has also been noted in a Taiwanese breast cancer population (Lee et al., 2008). Le et al. (2008) found that the peak incidence was among women in their 40s, with approximately 2% developing a nonbreast second primary cancer, with an average survival time of 2.87 years after the second cancer diagnosis. The risk of second primary colon cancer in patients following cancer of the breast has also been identified in a Connecticut, 1935-1982 population study (Harvey & Brinton, 1985). However, Harvey and Brinton (1985) failed to analyze BRCA status,

different ethnic groups, or time to event of the colon cancer. There has been a significantly increased risk of second primary rectal cancer (Observed/Expected = 1.97) in female breast cancer patients (Buiatti et al., 1997). This was observed in an Italian cohort population study that examined the incidence of second primary cancers in three cancer registries (Buiatti et al., 1997). Buiatti et al. (1997) also did not analyze different ethnic groups, BRCA status, or time to event of rectal cancer in the population. Certain subsets of breast cancer patients may demonstrate an elevated risk of developing second primary colorectal cancer (Kmet, Cook, Weiss, Schwartz, & White, 2003). Kmet et al. (2003) found that incidence of colorectal cancer was associated with a family history of breast cancer, high body mass index, and lobular breast cancer histology. Kmet et al. did not examine the BRCA status of the patients, ethnicity, and gender as specific risk factors. The risk of second primary contralateral breast cancer in BRCA1/BRCA2 mutation carriers with a first breast cancer has been documented (Molina-Montes et al., 2014). Molina-Montes et al. (2014) observed the risk of second primary contralateral breast cancer increases with length of time after the first breast cancer diagnosis in BRCA1/2 mutation carriers. The limitations of Molina-Montes et al.'s design included the exclusion of analysis of second primary cancer from other parts of the body system (e.g., pancreas, colon/rectum, endometrium, and cervix), ethnic groups, and time to diagnosis of second cancer. No studies were designed to analyze risk factors for time to diagnosis of a second cancer. These and other relevant studies are discussed further in Chapter 2.

My study fills this gap by examining the relationship between the risk factors age at diagnosis, ethnicity, and gender and time to diagnosis of a second primary cancer among women with breast cancer. Investigation of the risk factors and time to development of a second cancer after diagnosis with a BRCA germline mutation is needed to develop appropriate screening and treatment for breast cancer patients and survivors. Data on average time to diagnosis of second cancers for individuals with BRCA1/BRCA2 gene mutations would help clinicians to determine the best course of action for those newly diagnosed with a BRCA mutation and for breast cancer patients with BRCA mutations, thus supporting positive social change. Understanding the risk factors by the ethnicity, gender, and age of patients will assist clinicians in evaluating further screening options. In the study, application of the CPH model provided further insight based on time-to-event (diagnosis) in respect to the demographic variables gender, ethnicity, and age of diagnosis with BRCA1/BRCA2 mutation breast cancer for an association with time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, and/or bladder.

Summary

Among women, breast cancer is the most common malignancy and the second leading cause of cancer mortality (Singletary et al., 2004). The discovery of BRCA1/BRCA2 gene mutations has resulted in more appropriate targeting of preventive and screening strategies, even within families previously assumed to be similar with respect to breast cancer risk (Breast Cancer Family Registry, 2014).

Only one scholar has specifically analyzed age for time to diagnosis of pancreatic among female subjects with BRCA-related breast cancer (Mocci et al., 2013). No researcher has examined time to event and ethnicity as a risk factor for developing a second primary pancreatic, colorectal, endometrial, cervical, kidney, thyroid, or bladder cancer in patients previously diagnosed with BRCA1/BRCA2-mutation-related breast cancer using the composite endpoint approach. In this study, I further explored various risk factors contributing to the development of a second primary cancer in a breast cancer population.

Chapter 2 contains a review of the current literature on breast cancer epidemiology; BRCA1/BRCA2 mutations; and the pathology, diagnosis, and prognosis of breast, pancreatic, colorectal, endometrial, and cervical cancers. In Chapter 2, I present studies supporting the conceptual framework and study design. Modifiable risk factors such as hormone therapy radiation therapy, and oral contraceptives are outside the scope of the study and are covered only briefly, but the nonmodifiable risk factors of family history, age, ethnicity, and gender are addressed in more depth.

Chapter 2: Literature Review

The purpose of this study was to analyze the association of gender, ethnicity, and age of diagnosis of BRCA1/BRCA2-associated breast cancer with time to diagnosis of a second primary cancer, specifically pancreatic, colorectal, endometrial, and cervical cancer. This chapter contains a systematic and comprehensive review of the literature to determine the extant knowledge of the different research problems addressed in this study and to identify relevant previous and current studies on BRCA-related breast cancer and time to diagnosis with second cancers. Chapter 2 begins with a discussion of breast cancer epidemiology, including BRCA-mutation-related cancers. The recent literature on the pathophysiology and prognoses of breast, pancreatic, colorectal, endometrial, and cervical cancer and published studies on the relationship of gender, age, and ethnicity to BRCA-related carcinogenesis are presented and analyzed. I briefly discuss the nonmodifiable risk factors, methods of BRCA detection, cancer detection, staging and grading, and treatment. Next, I provide an analysis of the literature supporting the conceptual framework. Finally, I discuss other relevant studies on this BCFR dataset and other studies supporting my chosen methodology.

Literature Search Strategy

I employed CINAHL, MEDLINE, National Cancer Institute Comprehensive Cancer Databases, PUBMED, GOOGLE SCHOLAR, and Walden University dissertation ProQuest to conduct this literature review. During the search, I used the following major terms: *BRCA1*, *BRCA2*, *breast cancer*, *breast cancer epidemiology*, *diagnosis*, *second*

cancers, colon cancer, pancreatic cancer, endometrial cancer, cervical cancer, survival analysis, breast cancer prognosis, age, gender, ethnicity, and *Breast Cancer Family Registries (BCFR)*. The above search method generated numerous peer-reviewed published studies.

There is a gap that needs to be addressed related to the nonmodifiable risk factors of BRCA1/BRCA2 gene mutations and time to diagnosis of second cancers after stratification by age, gender, and racial and ethnic groups. Non-peer-reviewed studies were excluded, as were studies older than 10 years (2003 and earlier) unless they seminal.

Conceptual Framework

The conceptual framework of this study was based on empirical data on the mechanisms of action for how BRCA mutations may cause breast and other cancers. The functions of BRCA1 and BRCA2 genes are not fully elucidated. However, it is evident that they act as tumor suppressor genes, which are implicated in the cellular response to double strand DNA breaks, such as occurs normally as a result of damage to DNA (Goldberg & Borgen, 2006). Tumor tissue from heterozygotes for BRCA1 and BRCA2 mutations show a loss of heterozygosity, with the loss of the normal allele (Nussbaum et al., 2007). Many mutant alleles of BRCA1 and BRCA2 have now been catalogued. Several mutations have been found in the BRCA1 gene, distributed throughout the coding regions (Al-Mulla, Bland, Serrat, Miller, Chu, & Taylor, 2009).

Hereditary linkage investigations in families showing early onset of breast cancer contributed to locating BRCA1 on chromosome 17q21 and *BRCA2* on chromosome

13q12.3, and determining these as susceptibility genes for breast cancer (Le et al., 2011). Almost all known BRCA1 truncating mutations have demonstrated an association to disease, and a shortened BRCA1 protein leads to an increased risk for breast and ovarian cancer in women with a family hereditary susceptibility (Friedman et al., 1994). BRCA2 germline mutation results in truncated protein, conferring an increased risk of breast cancer among both females and males (Friedman et al., 1994). About 80% of cases of hereditary breast neoplasms are as a result of gene mutations of either BRCA1 (40-45% of cases) or BRCA2 (35-40%; Collins et al., 1995). Some of the remaining 20% of hereditary cases are associated with mutations of non-BRCA genes, such as those of Cowden syndrome (the PTEN tumor, suppressor gene), the Li-Fraumeni syndrome (TP53), ataxia telangiectasia (ATM), and Peutz-Jeghers syndrome (STK1/LKB1). These known genes do not account for 100% of hereditary breast cancers, which suggests the likelihood of finding other susceptibility genes in the future (Nussbaum et al., 2007).

Mutations occur continuously during cell division, and oncogenes and tumor suppressor genes are generally not inherently more prone to mutation than other genes. Strong positive selection for cell proliferation or increased cellular survival resulting from the mutation is what differentiates breast cancer gene mutations such as BRCA1 and BRCA2 from other mutations (Nussbaum et al., 2007). The phenotype of a breast cancer cell is uncontrolled and excessive proliferation, which ultimately allows even one mutant cell to develop into a life threatening disease. Mutations that allow one cell

among many to lose function, or die, have no phenotypic effects and are masked by the greater number of healthy cells in an organ or tissue (Nussbaum et al., 2007).

Although individuals with a strong hereditary susceptibility to cancer represent less than 5% of all patients with cancer, further elucidating the genetic basis of breast cancer has relevance for providing clinical management in affected families and for understanding breast cancer in general (Nussbaum et al., 2007).

There are several observations of loss of BRCA2 heterozygosity in tumors of the prostate, cervix, ovary, colon, male breast, and ureter, indicating the association between and increased risk of secondary cancers (Lancaster et al., 1996; Phelan et al., 1997). These findings for how BRCA gene mutations may predispose affected individuals to secondary cancers provided the framework for exploring time to diagnosis of a secondary cancer among those with BRCA-mutation-related breast cancer.

Breast Cancer

Risk Factors and Incidence

In the United States, breast cancer remains the most common type of neoplasm and is a cause of mortality among women (Le, Bhushan, & Tolles, 2011). The average age at diagnosis in the United States is 64 years (Nussbaum et al., 2007). Breast cancer risk varies from one population to another and is multifactorial (Satagopan et al., 2001). Modifiable risk factors include environmental exposure (Le et al., 2011), including radiation exposure at a young age such as in the treatment of Hodgkin disease

(Kleinerman, 2006), hormone therapy (Singletary et al., 2004), and obesity (Singletary et al., 2004).

Nonmodifiable risk factors include gender (Ferrone et al., 2009), ethnicity (Suchy et al., 2010), age (Al-Mulla et al., 2009), geographic location (Althuis, Dozier, Anderson, Devesa, & Brinton, 2005), and family history of breast cancer (Niell et al., 2004). Carcinoma rarely develops before 25 years of age in nonhereditary cases. Breast cancer is more commonly observed in premenopausal women with a family history of breast cancer (Mitchell, Kumar, Abbas, Fausto, & Aster, 2012), with increased risk based on the number of first-degree relatives with cancer. Claus et al. (1994) determined that the risk of female breast cancer increased three fold if any close relative was affected and up to 10 times if more than one first-degree relative was affected. The risks increased more when the disease onset is observed in first-degree relatives' 40-years-old or younger (Claus et al., 1994).

More than 2,000 mutations are associated with BRCA1 and BRCA2 (Thompson, & Easton, 2004). BRCA1 and BRCA2 mutations account for 3-10% of all hereditary breast cancers in susceptible population (Nussbaum et al., 2007). The BRCA1 gene mutation diagnosis is a risk factor for both breast and ovarian cancer, with an approximate risk of 80% of one or both types of cancer at 70 years (Nussbaum et al., 2007). BRCA2 gene mutations are associated with an 80% risk of being diagnosed with breast cancer, but less than a 10 % risk of ovarian cancer (Evans et al., 2009; Lakhani et al., 2004; Le et al., 2011; Nussbaum et al., 2007).

BRCA1/BRCA2 gene mutations together are implicated in about 70- 80% of hereditary breast cancers and sometimes even in nonhereditary breast cancer (Nussbaum et al., 2007). As many as 19% of all breast cancer cases may show a polygenic or multifactorial mode of inheritance, while a small proportion appear to be a result of dominantly inherited Mendelian predisposition to breast cancer (Claus et al., 1994). These families have in common certain features of familial cancer not found in sporadic cancer, including multiple affected family members, earlier age of onset, and frequent bilateral disease (Nussbaum et al., 2007). Dite et al. (2010) determined that cancer risk increased among relatives of patients with early diagnosis with BRCA1 and BRCA2 mutations. On the other hand, Loman, Bladstrom, Johanssonn, Borg, and Olsson (2003) demonstrated that the incidence of breast cancer among first-degree family members might increase as a result of other nongenetic risk factors.

This relationship with family history is mostly observed for inherited genes, including BRCA1, BRCA2, p53 (Li Fraumeni syndrome), ATM (ataxia-telangiectasia), and the gene causing Cowden disease (Mitchell et al., 2012). Others at higher risk of breast cancer include women with history of proliferative breast disease, especially when changes are atypical, and women with carcinoma of the contralateral breast or endometrium (Le et al., 2011). Pedigree analysis remains critical to ascertain the estimated risk of a patient with BRCA1 or BRCA2 gene mutation. A three-generation pedigree involving the patient (the proband), all the siblings, and parental and grandparental generations is a minimum requirement.

Gender. Gender-based risk factors for breast cancer are often related to hormones. Hormone-related risk factors that have been identified include early menarche and late menopause, indicating long reproductive potential (Chang-Claude et al., 2007); nulliparous women as compared to multiparous women, suggesting unremitting exposure to ovarian cycles (Cullinane et al., 2005); having the first child after the age of 30 (Cullinane et al., 2005); and obese postmenopausal women, which has been attributed to estrogen synthesis in fat depots (Mitchell et al., 2012). Obesity in younger women decreases the risk, due to an association with anovulatory cycles (Hernandez-Rey, 2014).

There has been a noted increase in estrogen-receptor positive breast cancers, mainly among young White women (DeShantis, Ma, Bryan, & Jemal, 2014). This implies differential hormonal risk factors among various groups. Women with a deleterious BRCA1 mutation are more likely to be diagnosed with triple negative cancers, which generally have poorer prognosis than other breast cancers (Singletary et al., 2004). Further exploration is needed to determine the significant risk factors for breast cancer and prognosis. Based on the importance of these nonmodifiable factors in breast cancer epidemiology, I included gender, ethnicity, and age as variables in this study.

Female gender is a well-known risk factor for breast cancer, but the risk for males is not negligible. My study included gender as a covariate, as it may influence the development of secondary cancers. Female breast cancer occurs 100 times more

frequently than male breast cancer, but male breast cancer has been associated with a higher mortality rate (Singletary et al., 2004).

Data are somewhat conflicting on whether the incidence of male breast cancer has changed over time. La Vecchia, Levi, and Lucchini (1992) determined that rates were relatively stable over the past 40 years. However, in a more recent study, the incidence of male breast carcinoma increased significantly from 0.86 to 1.08 per 100,000 population ($P < 0.001$) during the period from 1973 to 1998 (Giordano, Cohen, Buzdar, Perkins, & Hortobagyi, 2004). About 1,300 new cases of male breast cancer were diagnosed in the United States in 2003, with approximately 400 deaths (Jemals et al., 2003). In 2014, 2,360 males were diagnosed, including 430 deaths (NCI, 2014). Some male breast cancer cases have been identified among individuals without a family history (Csoka et al., 1999). Males diagnosed at a later age and were more likely to have lymph node involvement, suggesting a more advanced stage at diagnosis (Giordano et al., 2004). Recognizing the risk factors for male breast cancer is imperative to early diagnosis and better health outcomes.

There may be geographical differences for male breast cancer incidence (Contractor, Kaur, Rodrigues, Kulkarni, & Singhal, 2008). Male breast cancer accounts for only 1% of total breast cancer diagnoses in most Western countries (Contractor et al., 2008). However, a higher proportion of cases in men were recorded in some countries (Amir, Moshiro, & Kwesigabo, 1996; Sasco, Lowenfels, & Pasker-de long, 1993). In Tanzania, 7% of breast cancers were reported in men (Amir et al., 1996). O;malley,

Prehn, Shema, and Glaser (2002) found higher incidence of male breast cancer in the United States and United Kingdom than Japan and Finland. There are limited data on male breast cancer from Africa. The incidence rate in the East African country of Uganda is rising (Contractor et al., 2008). In Zambia, male breast cancer accounts for about 15% of all breast cancer cases (Smigal et al., 2006), while it accounts for 6% in Tanzania (Ihekwaba, 1994). The World Cancer Research Fund International (2014) reported that the European incidence rate of breast cancer in 2012 had doubled that of Africa; North America presented the overall highest incidence rate of 92 per 100,000 population in the United States, closely followed by 80 per 100,000 population in Canada.

Known male breast cancer risk factors include heritable mutations, including BRCA, and imbalances in hormonal levels (Ottini et al., 2003; Struewing et al., 1995). In an investigation of 76 men with a family history of breast cancer, Frank et al. (2002) found that 11% had BRCA1 mutations, but BRCA2 was not assessed in the study. Others have reported a much lower prevalence of BRCA1 mutations in males compared to BRCA2 (Basham et al., 2002; Ottini et al., 2003). Ottni et al. (2003) observed 16% of Italian men with breast cancer had either BRCA1 or BRCA2, with 75% of the cases having BRCA2 mutations (Ottini et al., 2003). Basham et al. (2002) determined that out of 19 cases of subjects with male breast cancer, none had BRCA1 mutations, and five cases had BRCA2 mutations. This suggests a possible stronger role for BRCA2 than BRCA1 in male breast cancer. The prevalence of BRCA2 mutations in men without a strong family history of breast cancer may range from 4% to up to 40% (Basham et al.,

2002; Ottini et al., 2003). In families with a history of both female and male breast cancer, the presence of BRCA2 mutations has been reported to be as high as 60-76% (Osorio et al., 2000).

Hormone status as a risk factor is not limited to females. There is a documented relationship between conditions that may be related to hormonal levels and risk of male breast cancer. In a case control study of 227 men, Thomas et al. (1992) reported an increased risk of male breast cancer with a history of undescended testes (relative risk [RR] =11.6), orchitis (RR = 2.0), infertility (RR = 2.3), and benign breast conditions (RR = 2.5). Thomas et al. also reported some probable nonhormonal risk factors, including Jewish ancestry (RR = 2.1), congenital inguinal hernia (RR=2.3), and amphetamine use (RR = 2.9). Similar results were obtained in a meta-analysis of risk factors for male breast cancer, with previous benign breast pathology, Jewish ancestry, and testicular pathology all predispositions to breast cancer (Sasco et al., 1993).

Geographical location and ethnicity. There are data demonstrating geographical and ethnical disparities in overall breast cancer epidemiology (Nussbaum et al., 2007). Historically, in the United States, White women over the age of 40 have borne the highest risks of developing breast cancer. According to population-related epidemiological investigations, more than 9% of all women in North America are at risk of developing breast cancer (Claus, Risch, & Thompson, 1994). White women in the United States have incidence rates 20% to 40% higher than in non-White women (Claus et al., 1994). Incidence in some populations has not remained stable over time. In recent years, rates

for Black women have been approaching those for White women, while incidence among Hispanic women has decreased (DeShantis, Ma, Bryan, & Jemal, 2014). Black women less than 40 years of age have a higher incidence rate than their young White counterparts (Jemals et al., 2003).

Mortality rates from breast cancer also differ by ethnicity and geography. In the United States, mortality rates are highest for Black women, followed by White, Hispanic, American Indian/Alaska Native, and Asian/Pacific Islanders (American Cancer Society, 2003). Globally, most of the 300,000 deaths due to breast cancer in 1990 were in developed countries (Lacey, Devesa, & Brinton, 2002), with death rates lowest in Asia, moderate in South America and Eastern Europe, and highest in North America and Western Europe (Lacey et al., 2002). Overall, mortality from breast cancer has dropped in all ethnic groups except American Indians and Alaskan natives. These trends suggest some etiologic heterogeneity and the different effects of various risk factors that may differ among certain groups (DeSantis, 2014).

Ethnicity is an important variable in studying hereditary mutations such as BRCA because the mutations may vary between populations. John et al. (2011) found differing percentages of frameshift, missense, nonsense, and splice mutations between ethnic groups. Tamboom et al. (2010) found three clinically important mutations in the BRCA1 gene and two clinically important mutations associated with BRCA2 gene in an Estonian population. BRCA1 founder mutations are prevalent in certain populations (Kadouri, 2007). Founder mutations are mainly observed among ethnic groups that live in relative

isolation, such as the people of Iceland or certain communities of Jewish people (Singletary, 2004). According to haplotype analysis, these mutations have the same ancestor. A higher prevalence of deleterious BRCA1 and BRCA2 gene mutations appear in the Ashkenazi Jewish population than in the general population (Singletary, 2004). Higher prevalence of specific deleterious BRCA1 and BRCA2 mutations have also been observed in other ethnic and geographical populations, such as the Icelandic people, the Norwegians, and the Dutch (NCI, 2014). Furthermore, the prevalence of harmful BRCA1 and BRCA2 mutations may be different in individual ethnic and racial groups in the United States, including African Americans (Malone et al., 2006), Asian Americans, non-Hispanics, and Hispanics (John et al., 2007). I stopped reviewing here due to time constraints.

Among the Ashkenazi Jewish population, three mutation types (BRCA1 185delAG, BRCA1 5382insC, and BRCA2 6174delT) are well documented (Moslehi et al., 2000). The 185delAG mutation is one of the most frequent BRCA1 mutations found among the Ashkenazi Jews (Neuhaussen et al., 1998). Two other founder mutations segregate in this ethnic group: the BRCA1 5382insC and the BRCA2 6174delT mutations (Roa, Boyd, Volcik, & Richards, 1996). At least one of the three founder mutations can be found in more than 2% of the Ashkenazi Jewish population and in about 12% of the Ashkenazi Jewish breast or ovarian cancer patients with no family history (Abeliovich et al., 1997). Subsequent screenings have shown other BRCA1 founder mutations in the Netherlands (Petrij-Bosch et al., 1997); Norway (Dorum, Hovig, Trope, Inganas, &

Moller, 1999) Sweden (Johannsson et al., 1999); and the Yorkshire/Humberside population in United Kingdom (Al-Mulla et al., 2009). Al-Mulla et al. (2009) also reported of identifying 14 new BRCA1/BRCA2 gene mutations among the Yorkshire/Humberside population.

Papelard et al. (2000) investigated BRCA1 prevalence in 642 Dutch breast cancer patients in a hospital-based population. Four patients carried the Dutch founder deletion of exon 22. All mutation carriers were under 50 years-of-age at diagnosis of the first breast cancer, and five did not have any relative with breast cancer (Papelard et al., 2000). The estimated prevalence of breast cancer in the general population in the Netherlands attributable to BRCA1 mutations is 2.1%, but specifically for less than 40 years-of-age, the prevalence is 9.5% and under 50 years-of-age the prevalence is 6.4%. This supports a higher risk of younger breast cancer diagnosis for BRCA carriers in the Dutch population.

Study design is an important consideration in determining ethnic differences in breast cancer incidence. Gathani et al. (2014) conducted a prospective cohort study on Black, White, and South Asian women using Cox regression models to calculate adjusted relative risks (RR). Initial findings indicated prevalence differed substantially by ethnicity ($P<0.001$), with South Asian (RR=0.82, 95% CI 0.72–0.94) and Black women (RR=0.85, 0.73–0.98) at a lower risk than White women (Gathani et al., 2014) after adjustment for age and region of residence. However, after additional adjustment for known breast cancer risk factors, incidence was similar to that of Whites, both in South

Asians and in Blacks. Different interpretations of findings for differences between ethnicities are possible and study design is an important factor. These data underscore the need for my study, which will further investigate the role of ethnicity in BRCA related cancer epidemiology.

Time to diagnosis and tumor type may also differ by ethnicity and by mutation type. A cohort study among Japanese women determined the mean age at the time of diagnosis for BRCA1 and BRCA2 carriers to be 44 years compared to 54 years for the control group. The incidence of bilateral tumor was significantly higher in BRCA1 at 32 percent and BRCA2 was associated with 29 percent compared to 6 percent observed in the control group (Noguchi et al., 1999). BRCA1-associated hereditary cancers in this study demonstrated an increase in the risk of solid-tubular type tumors and a significant increase in histologic grade 3 tumors ($p<0.01$) compared with the control group. BRCA1 related familiar breast cancers in Japanese women demonstrated biologically aggressive phenotypes, while BRCA2 associated familiar breast cancer did not demonstrate distinguishable clinical or pathologic characteristics in comparison with the sporadic cancers. These findings suggest that recognizing differences in ethnicity and mutation status is essential to developing appropriate screening and follow up protocols.

Age. Incidence of both female and male breast cancer increases with age (Ewertz, Holmberg, & Karjalainen, 1989). Early studies demonstrated that by seventy years of age, women have a more than eighty percent risk of developing breast cancer if heterozygous for BRCA1 or BRCA2 mutations (Nussbaum et al., 2007). However, age as

a risk factor is intertwined in some ways with ethnicity/geography and gender. Age older than 40 has been shown to be a risk factor for White women, but for Black women, being younger than 40 years of age increases risk of breast cancer (Jemals et al., 2003). Heredity and family history are a major influence on the age at which risk is highest (Mitchell, Kumar, Abbas, Fausto, & Aster, 2012). Hormonal status is also difficult to separate from age. A younger woman who is obese will have a lower risk than an older woman who is obese (Hernandez-Rey, 2014), while a woman who put off childbearing to later years is at higher risk due to more ovulatory cycles (Cullinane et al., 2005).

Increasing age remains the most vital and significant predictor of breast cancer risk. Most cancers of the breast occur after 50 years of age (Singletary et al., 2004). However, BRCA1 and BRCA2 mutation related breast cancer develops often before 50 years of age (Papelard et al., 2000; Sing et al., 2000). Lifetime risk, as derived from incidence tables formulated through the NCI-SEER registry, is quoted as 1 in 9 when lifetime is considered up to 85 years of age or 1 in 8 when lifetime is considered beyond after 95 years of age. During clinical counseling sessions, lifetime and age specific rates for women at average risk are crucial parameters against which to compare quantitatively elevated risk figures (Singletary et al., 2004).

Sing et al. (2000) determined that Chinese women are often diagnosed with BRCA1 and BRCA2 before 50 years of age. Sing et al. (2000) examined the prevalence of BRCA1 mutations in 92 Chinese breast cancer patients in Singapore with a history of cancer of the breast before the age of 40. All six disease-causing mutations occurred in

women less than 40 years (8.6%) with three occurring in patients under 35 years (13.6%). Missense mutations of unknown significance were found in three patients. Two of the ten women with affected relatives under 40 years had BRCA1 mutations. The prevalence of BRCA1 mutations in Chinese subjects with early-onset breast cancer is similar to that observed in Caucasian women (Sing et al., 2000). A limitation of the Singh et al. study is the lack of specific intent to analyze age as a risk factor. My study will further examine age of diagnosis of BRCA mutation related breast cancer and time to diagnosis of a second primary cancer.

Second Primary Cancers and BRCA Genes

Individuals with breast cancer have been reported to be more susceptible to developing additional malignancies, and these second cancers may adversely impact prognosis and survival time (Lee et al., 2008; Hemminki et al., 2005). A second cancer which develops after diagnosis with breast cancer may be either secondary or a second primary cancer. Secondary cancer occurs when the primary or initial cancer cells spread or metastasize to another part of the body (Singletary et al.., 2004) resulting in the formation of a new tumor with the same cell type as the original cancer. Breast cancer cells can metastasize from the primary cancer site through the lymphatic cells or the bloodstream (Singletary et al., 2004). Symptoms depend on the specific part of the body where metastasis has occurred (Cancer Research UK, 2014).

The risk for developing second cancers may be significant for patients diagnosed with breast cancer before age 40 (Lee et al., 2008; Lee et al., 2006). Lee et al. (2008)

determined an increased risk for developing a second primary malignancy in a Taiwanese breast cancer population. Second cancers of the breast were excluded in order to rule out secondary cancer of the same cellular origin. Results indicated excess risk for cancer of the bone, uterus, ovary, non-melanoma skin, thyroid, esophagus, kidney, lung, leukemia, and lymphoma. Lee et al. found the peak incidence was among women in their 40s, with approximately 2% developing a non-breast second primary cancer, with an average survival time of 2.87 years after the second cancer diagnosis (Lee et al., 2008). This poor prognosis for individuals with a second cancer diagnosis highlights the significance of identifying those at risk as early as possible, in order to improve health outcomes for this population. A limitation of the Lee study is that it was not designed to determine any association with mutations such as BRCA. The Lee study did not report any association with pancreatic or colon cancer, which may be due to the specific focus on a Taiwanese population and differential risks. Although Lee did not analyze BRCA status, the finding for a higher risk with younger age is in line with the increased likelihood of those with a BRCA mutation to develop cancer at a younger age. Additional studies on other ethnic populations would be useful to characterize this risk.

Several studies support an association between younger age and second cancers in a *BRCA* population (Mocci et al., 2013; Hemminki et al., 2005; Brose et al., 2002; Johannesdottir et al., 1996). Mocci et al. aimed to estimate pancreatic cancer risk in high-risk breast cancer families according to the BRCA mutation status. The authors applied a retrospective cohort analysis in order to ascertain the standardized incidence ratios (SIR)

for pancreatic cancer. Eligibility was based on families with ≥1 breast cancer case tested for mutations in BRCA1 and/or BRCA2. They observed that the women diagnosed with a BRCA mutation related breast cancer before 50 years of age were at a higher risk for developing a second cancer (Mocci et al., 2013). Mocci and colleagues noted BRCA1 mutation carriers were at increased risk of pancreatic cancer (SIR= 4.11; 95% confidence interval [CI], 2.94-5.76) as were BRCA2 mutation carriers (SIR=5.79; 95% CI, 4.28-7.84) (Mocci et al., 2013). The study was limited in that it did not examine colorectal cancer and familial pancreatic cancer risk estimate based on many ethnic groups. My study will further examine certain risk factors, including age of diagnosis, gender, ethnicity, and time to event of second primary cancer, pancreatic, colorectal, endometrial and cervical, among patients with breast cancer. Further studies are needed to elucidate the correlation between BRCA mutations and pancreatic cancer.

Hemminki et al. (2005) investigated the risks for second discordant tumors after male breast cancer in 3,409 male subjects. Data were obtained from 13 cancer registries using "standardized incidence ratios (SIR) adjusted for age, year and registry were calculated using indirect standardization methods. Exact confidence intervals (CI) around the SIR were calculated assuming a Poisson distribution for the observed number of neoplasms. Among the study cases, 12.5% were diagnosed with a second neoplasia other than breast cancer. There was a significant risk of a second primary neoplasia affecting either the small intestine, rectum, pancreas, skin (non-melanoma), prostate; and lymphohaematopoietic system. Hemminki and colleagues findings suggest that BRCA2

(and to some extent BRCA1) mutations may explain the findings for pancreatic and prostate cancers (Hemminki et al., 2005). Hemminki and colleagues did not examine the time to event of the various second cancers. My study will examine time to diagnosis of second cancer, pancreatic and colon and association with certain risk factors such as age of diagnosis, ethnicity and gender.

In a study to estimate BRCA1-related cancer risks for individuals ascertained in a breast cancer risk evaluation clinic, Brose et al. (2002) used an observed and age-adjusted cancer risk estimates to determine and analyze 483 BRCA1 mutation carriers in 147 families identified in two academic breast and ovarian cancer risk evaluation clinics. Brose et al. (2002) noted the mean "age at female breast cancer diagnosis in this study of BRCA1 mutation carriers, as in many others, was 42 years (95% CI = 40 to 44 years), and the average age at ovarian cancer diagnosis was 52 years (95% CI = 50 to 53 years). These ages are 20 and 10 years younger, respectively, than population averages. The average age at male breast cancer diagnosis was 53 years (95% CI = 45 to 60 years), compared with 69 years in the general population. The average age at colon cancer diagnosis was 65 years (95% CI = 59 to 71 years), compared with 72 years in the general population found that by 70 years of age, the risk among BRCA1 carriers of being diagnosed with ovarian cancer was 40.7%" (p. 1369). Brose et al. (2002) also observed a twofold increased risk of colon cancer, threefold risk of pancreatic cancer, fourfold risk of stomach cancer, and 120-fold increased risk of fallopian tube cancer among BRCA1 mutation carriers with breast cancer in comparison with the SEER Program population-

based estimates. A limitation is the study did not include BRCA2 carriers in the study design and analysis. Also, the Brose et al.'s study was not designed for patients with BRCA related breast cancer, but for families that had BRCA1 mutants identified. The above findings underscores the need for this study to investigate the role of age at diagnosis of BRCA mutation related breast cancer and time to event of diagnosing a second cancer in this susceptible population.

In order to ascertain the prevalence of BRCA2 mutations in Icelandic breast and ovarian cancer patients and association with second cancer, Johannesdottir et al. used the biopsy data from breast tumor. All available DNA samples of patients collected from nuclear pellets of patients diagnosed in the years 1989-1994 were included in the study. DNA from patients diagnosed with cancer other than breast and prostate was obtained from the University Hospital Iceland tumor bank. The control group were randomly selected DNA samples from subjects in the Iceland National Diet Survey (Johannesdottir et al., 1996). They determined the frequency of the 999del5 BRCA2 mutation in an

Icelandic control population and four groups of patients diagnosed with breast cancer, ovarian cancer, prostate cancer, and any other cancer. The findings showed that BRCA2 conferred a very high risk of breast cancer and appears to be responsible for a substantial fraction of breast and ovarian cancer in Iceland, but only a small proportion of other cancers (endometrium, colon, stomach, rectum, testis and thyroid) (Johannesdottir et al., 1996). The study was limited by non-inclusion of BRCA1 patients in their study design and also was not designed to study the time to event of second cancers. My study

will further examine time to event of second cancer, pancreatic and colon and association the risk factors, age of diagnosis, ethnicity and gender.

The literature demonstrates that aside from breast cancer, BRCA1 and BRCA2 gene mutations are associated with multiple other types of cancer, including endometrial (Shu et al; 2014), cervical (Rheim, Fisher, Bosse, Wappenschmidt, & Schmutzler, 2007), ovarian (Evans et al., 2009), colon (Kadouri et al., 2007; Brose et al., 2002), pancreatic (Mocci et al., 2013; Al-Mulla et al., 2009), bladder (Neveling et al., 2007), prostate (Hemminki et al., 2005; Johannesdottir et al., 1996), uterine (Thompson, Easton & the Breast Cancer Linkage Consortium, 2002), stomach (Brose et al., 2002), fallopian tube (Brose et al., 2002), and endometrial (Johannesdottir et al., 1996). The following sections discuss the literature on pancreatic, colorectal, endometria, and cervical cancer, specifically.

Pancreatic Cancer. Pancreatic cancer is the fifth leading cause of cancer mortality in the United States (Murphy et al., 2002). Each year about 40,000 pancreatic adenocarcinomas are diagnosed in the United States (Lowery et al., 2011). Pancreatitis usually occurs quickly while chronic pancreatitis occurs after several inflammatory insults to the pancreas over time leading to permanent damage (Schneider & Szanto, 2006). Although patients with chronic pancreatitis are predisposed to having pancreatic cancer, pancreatic cancer is most likely the result of the common risk factors of smoking, alcohol consumption, and gene mutations (Le et al., 2011). The overall incidence in the United States has been stable among men since 1993, with a slight 0.6 % yearly increase

among women since 1994 (Cancer Facts and Figures, 2012). Globally, most countries have a recorded annual incidence rate of 8-10 cases per 100, 000 persons, while about two cases of pancreatic cancer per 100, 000 are recorded annually in India (Dragovich, 2014). The average person has less than a 1% lifetime risk for this disease, but carcinoma of the pancreas accounts for 5 % of all cancer deaths in the United States (Dragovich, 2014). Peak incidence is between 60 and 80 years of age, and the 5-year survival is less than 4 % (Mitchell et al., 2012).

About 60% of the time, the carcinoma arises in the head of the pancreas, causing obstructive jaundice; somewhat less often it originates in the pancreatic body (15 %) or pancreatic tail (5 %), and 20% is diffuse or widely spread (Schneider & Szanto, 2006). Carcinoma involving the pancreatic tail can cause islet destruction and secondary diabetes mellitus (Schneider & Szanto, 2006). Tumors may be small and ill-defined or large (8-10 cm), with extensive local invasion and regional metastasis. Clinical characteristics show insidious growth over many years. About 85% of the carcinomas of the pancreas are unresectable, with poor prognosis. First year mortality exceeds 80%.

Weight loss and pain are typical presenting symptoms; obstructing jaundice with palpable gallbladder develops with tumors in the Head of Periampullary region (Le et al., 2011). Massive metastasis to the liver usually occurs through splenic vein invasion. It can also metastasize to the stomach, duodenum, colon, or any abdominal cavity surface during characteristic peritoneal spread (Dragovich, 2014). Migratory thrombophlebitis

may occur with pancreatic and pulmonary neoplasm or other visceral cancers (Mitchell et al., 2012).

Although the risk for pancreatic cancer is small among the general population, several studies established an association between BRCA gene mutations and increased risk for pancreatic cancer (Ferrone et al; 2009; Mocci et al., 2013). Ferrone et al. (2009) found 1.3% of Jewish patients who had a resection for pancreatic cancer had BRCA1, and 4.1% had BRCA2 germline mutations. There was no age difference or other differences in clinicopathologic characteristics. The Ferrone et al.'s study was not designed to look at pancreatic cancer as a second primary cancer after diagnosis with breast cancer. However, Ferrone reported previous breast cancer in 24% of the study subjects, suggesting that there is a correlation that needs further exploration.

Several researchers have found higher risk of pancreatic cancer for BRCA2 (Mocci et al., 2013; Goggins et al., 1996; Van Asperen et al., 2005). Germ-line BRCA2 mutations are the most common inherited genetic alteration known in hereditary pancreatic cancer, but BRCA is not the only gene related to pancreatic cancer. Greater than 90% of pancreatic cancers carry a *K-ras* mutation and 60 to 80% demonstrate mutations in *p53* (Mitchell et al., 2012). However, these genes are outside the scope of my study, and remain a potential confounder for pancreatic cancer cases in my study.

Some researchers have found significance for both BRCA1 and BRCA2 for risk of pancreatic cancer. Lowery et al. (2011) found that individuals who carried either BRCA1 or BRCA2 had increased risk of pancreatic cancer. Mocci et al. (2013) analyzed

the NCI- BCFR data of 5,799 families with at least one breast cancer case, testing for mutations in BRCA1 and BRCA2. Family members with at least one BRCA1 and/or BRCA2 case were at increased risk of pancreatic cancer, regardless of number of members with early-onset breast cancer adenocarcinoma.

A National Familial Pancreas Tumor Registry (NFPTR) study sought to identify the germline mutations associated with increased risk for pancreatic cancer. Murphy et al. (2002) selected patients with pancreatic cancer from kindreds enrolled in the NFPTR containing three or more cases of pancreatic cancer, where at least two of the affected persons were first-degree relatives. Murphy et al. analyzed samples representing 29 kindreds for four tumor suppressor genes, including BRCA2. Of the mutations studied, only BRCA2 was significantly associated with pancreatic cancer. However, Murphy et al. did not analyze other potential genes including BRCA1, *K-ras*, or *p53* in this study. Two of the five BRCA2 mutation carriers also reported a family history of breast cancer (Murphy et al., 2002), further supporting the need for my study to analyze the relationship between breast cancer and pancreatic cancer in the BRCA carrier population.

The above studies highlight the association that exists between BCRA mutations and increased susceptibility to both breast and pancreatic cancer. However, few if any studies have specifically examined the development of pancreatic cancer after diagnosis with breast cancer in a BRCA positive population. The proposed study fills a gap in the literature by reporting the time to event of pancreatic cancer among BRCA1/BRCA2 cases after initial diagnosis with breast cancer.

Colorectal Cancer. Annually, there are approximately 1 million cases of colorectal cancer and about 500, 000 estimated deaths globally (Boyle & Leon, 2002). The Surveillance Epidemiology and End Results Program (SEER, 2014) estimated that in 2011, approximately 1,162,426 individuals were living with colon and/or rectal cancer in the United States. Colorectal cancer affects more than 150,000 individuals every year in the United States alone and is responsible for 15 % of all cancers. Cancer of the colon is the third most common cancer, the third most deadly cancer in the United States, and the only cancer that occurs with equal frequency among men and women (Le et al., 2011; NCI, 2014). Most patients are greater than 50 years of age, and approximately 25 % have a family history (Le et al., 2011). About 4.8 percent of men and women living in the United States may be diagnosed with colon or rectal cancer at some point in life (SEER, 2014).

It can be difficult to differentiate cancers of colon and rectum in mortality statistics. According to NC1 (2014) there were 96,830 colon cancers and 40,000 rectal cancers, and colorectal cancer as a whole resulted in approximately 50,310 deaths. There are significant differences in incidence in multiracial/ethnic countries among ethnically or racially defined populations (Boyle, 1989). Boyle and Leon (2002) found the highest incidence in the United States, Canada, Japan, and New Zealand. These high rates were found in a variety of population groups including Blacks in Detroit (34.9 per 100,000), Los Angeles (34.8), San Francisco (33.8), Atlanta (32.4), and New Orleans (31.4), Hawaiian Japanese (34.4), Hawaiian Whites (32.7) and non-Maori in New Zealand

(31.2). Data from SEER (2014) incidence rates (per 100,000) reported as Blacks (47.5), Whites (37.3), Asian/Pacific Islanders (32), American Indian/Alaskan (35.5), and Hispanics (31.2).

Colorectal cancer involves the epithelium of the colon or rectum and is one of the most common forms of cancer (Le et al., 2011). Invasive adenocarcinoma is a malignant lesion with metastatic potential because it has crossed into submucosa, which contains lymphatics (Le et al., 2011). Endoscopic removal of a malignant polyp is adequate if the invasive adenocarcinoma is superficial and there is no vascular or lymphatic invasion (Mitchell et al., 2012). There is substantial evidence to support a genetic factor for familial colon cancer (Nussbaum et al., 2007).

A small proportion of colon cancer cases, with an annual incidence of 10,000 cases, are due to Familial Adenomatous Polyposis (*FAP*). *FAP* is an autosomal dominant mutation of the *APC* gene on chromosome 5q. *FAP* (Nussbaum et al., 2007). In nearly 70% of adenomatous polyps (precursors to colorectal cancer) in individuals without *FAP*, the two-hit model of tumorigenesis has been confirmed by the loss of both copies of *APC* in the adenoma, but not in the surrounding normal tissue (Nussbaum, et al., 2007). About 90% of adenomas are found in the colon; they may also occur in the stomach and small intestine. Another proportion of familial colorectal cancer cases are observed in individuals with the hereditary non-polyposis colorectal cancer (HNPCC/Lynch syndrome), an autosomal-dominant mutation of DNA mismatch repair genes. Approximately 80% will progress to colorectal cancer (Le et al., 2011).

Most sporadic colorectal cancers are thought to arise in polyploid adenomas. Diet may be an important risk factor (Mitchell et al., 2012). Colorectal cancer risk is associated with excess energy intake relative to requirements, low vegetable fiber intake, high content of refined carbohydrates, and high intake of red meat and decreased intake of protective micronutrients (particularly vitamins A, C, and E). Such diets may cause increased exposure to bile acids and bacterial degradative by product. However, a causal relationship with diet has not been substantiated (Mitchell et al., 2012).

Clinically, early onset of colon cancer and premalignant adenomatous polyps are usually asymptomatic, and this makes them difficult to discover until an advanced stage of colon cancer presenting with symptoms (Cappell, 2008). Symptoms of colorectal cancer include fatigue, weakness, iron deficiency anemia, abdominal discomfort, progressive bowel obstruction, and liver enlargement (Schneider & Szanto, 2006). Prognosis depends on the extent of invasion at diagnosis. Five-year survival depends on the depth of penetration and lymph node involvement and ranges from 100 % for lesions limited to the mucosa to 25 % for extensive invasive tumors.

BRCA mutation status has been demonstrated to be a risk factor for colorectal cancer, particularly for younger women (Brose et al; 2002; Ford, Easton, Bishop, Narod, & Goldgar, 1994; Phelan et al., 2013; Suchy et al. 2010). Brose et al. (2002) noted a twofold increased risk of colon cancer in BRCA1 mutation carriers' families with breast cancer risk. Ford et al. demonstrated that carriers are at increased risk of colon and prostate cancer, which may be of clinical significance in certain families if the risk is

associated with specific mutation (Ford et al., 1994). However, few studies have specifically looked at the epidemiology of colon cancer as a second primary cancer after diagnosis with breast cancer.

Suchy et al. (2010) examined 2,398 Polish subjects with colorectal cancer for three known Polish BRCA1 founder mutations (C61G, 4153delA, and 5382insC). A BRCA1 mutation was present in 0.42% of unselected cases of colorectal cancer and in 0.48% of controls. The mutation frequency was slightly higher (0.93%) in cases who reported a family history of colon cancer in a first- or second-degree relative. A BRCA1 mutation was observed in 0.82% of cases who were diagnosed with colorectal cancer at age 60 or earlier. The mean age at onset in carriers was 7 years younger than in non-carriers (57.0 years vs. 64.0) and the difference was significant ($P = 0.05$). Suchy et al. did not report on whether the subjects had breast cancer, but these findings support a higher risk for younger patients with BRCA mutations and potential for developing a second primary colon cancer in this susceptible population. My study examined the time to event of second primary colon cancer diagnosis in patients after initial diagnosis with BRCA mutation related breast cancer.

Phelan et al. (2013), observed colorectal cancer cases in both BRCA1 and BRCA2 carriers. Findings demonstrated an increased risk of colorectal cancer among female carriers of BRCA1 gene mutation who were below 50 years of age, but not in older women or individuals with BRCA2 mutations. Phelan et al. (2013) did not specifically aim to examine the incidence of colorectal cancer as a second primary cancer

among women with BRCA1 or BRCA2 mutation related breast cancer. The above findings support an association between early onset of colorectal cancer and BRCA mutations. However, the association with the development of second primary colorectal cancer after diagnosis with BRCA related breast cancer needs more elucidation. In the proposed study, I will examine the time to event of colon cancer diagnosis in patients after initial diagnosis with BRCA mutation related breast cancer.

Endometrial Cancer. Endometrial cancer is the most common cancer of the female reproductive system, accounting for 6% of all the cancers among women in the United States (National Cancer Institute (NCI), 2014). Endometrial cancer usually begins in the cells of the inner lining of the uterus (the endometrium) and can be divided into squamous cell carcinoma, adenocarcinoma and undifferentiated carcinoma, depending on the appearance of the cells under the microscope (American Cancer Society, 2015). Some risk factors associated with increased risk of endometrial cancer include genetics, postmenopausal estrogen therapy, obesity, tamoxifen use, early menarche and late menopause (NCI, 2014). Incidence rates have remained steady since 2002, whereas the mortality rates since 2001 have been rising gradually. In the United States, African American women have a slightly higher incidence rate compared to White women and twice the mortality rate compared to other ethnic/racial populations (NCI, 2014). However, Caucasian women have a 2.88% lifetime risk of developing uterine cancer compared to African American women, with lifetime risk of 1.69%. African American women are more likely to have non-endometrioid, high-grade tumors and a more

advanced stage of disease at the time of diagnosis compared to Caucasian women who have similar demographics (Oliver et al., 2001). Menopausal women account for the majority of individuals diagnosed with endometrial cancer, with an average age of diagnosis of 60. Endometrial cancer is rarely observed in women less than 40 years of age (5-10%) (OncoLink, 2015). According to the Surveillance, Epidemiology, and End Results Program (SEER, 2015) age-adjusted data based on 2008-2012 cases and deaths, there were 25.1 per 100,000 new cases of endometrial cancer in the United States per year; while the number of deaths was 4.4 per 100,000 women per year. 2012 prevalence data from SEER (2015) estimated that 621,612 women were living with endometrial cancer in the United States.

Patients with an initial diagnosis of breast cancer may have an increased risk of developing a particular type of endometrial cancer later (Gehrig et al., 2004). Gehrig et al. (2004) determined that women with breast cancer who were later diagnosed with endometrial cancer demonstrated a 2.6-fold increased risk of developing a uterine serous carcinoma as compared to an endometrioid carcinoma.

The association between germline mutations in BRCA genes and the risk of endometrial cancer remains unclear, but several case reports of endometrial carcinoma in women with a BRCA mutation exist (Oh, Kim, Kim, & Kim, 2015; Levine et al., 2001). Inherited mutations in the BRCA1 or BRCA2 genes are associated with a greatly increased lifetime risk of breast and endometrial cancers (Shu et al., 2014) and cervical (Rheim et al., 2007).

Levine et al. (2001) conducted a retrospective cohort study with 199 consecutive Ashkenazi Jewish patients with endometrial carcinoma in in a New York City Cancer Center to examine the relationship between BRCA and endometrial carcinoma. All the study participants were genotyped for the three BRCA founder mutations (185delAG and 5382insC in BRCA1 and 6174delT in BRCA2) that exist in this population, and the case frequency was compared to the known population frequency of these mutations. BRCA mutations were observed in 1.5% of the 199 patients; one in BRCA1 and two in BRCA2, compared to an expected frequency of 2.0%. Relative risk of endometrial carcinoma associated with BRCA mutation, as estimated by the odds ratio, was calculated as 0.75 (95% CI = 0.24–2.34). The above findings imply that despite the relationship between BRCA and endometrial carcinoma, for people with a germline BRCA mutation, the lifetime risk of endometrial cancer may be low.

Shu et al. (2014) investigated 525 subjects to determine whether there was an increased risk of uterine cancer among patients with BRCA mutations. The prospective study aim was to determine whether the risk of uterine corpus cancer following risk-reducing salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations were greater than that seen in the general population. Subjects obtained from Memorial Sloan Kettering Cancer Center in New York were followed prospectively via annual questionnaires and medical record review for a median of 5.8 years. Shu and colleagues reported an aggressive form of uterine cancer, either serous carcinoma, carcinosarcoma, or leiomyosarcoma developed in 4 of the 296 women with a BRCA1 mutation, a 2.1%

risk over 10 years. This risk is approximately 26-fold higher than expected in the general population (Shu et al., 2014). None of the women with a BRCA2 mutation were diagnosed with uterine cancer. These data suggest that BRCA1 may be responsible for an increased risk of an aggressive form of uterine cancer, but there is insufficient data on the potential relationship to endometrial cancer. The study was not designed to look at time to diagnosis of second primary cancers in a population with breast cancer. My study further investigated association of BRCA1 and BRCA2 with age, and ethnicity and the time to event of endometrial cancer among the study population.

Cervical Cancer. Cervical cancer is strongly associated with the Human Papilloma Virus (HPV). In the United States, the incidence rates of cervical cancer have declined 45 percent and mortality rates have declined 49 percent since 1980. According to the National Vital Statistics System (2013), the age-adjusted cervical cancer death rate was 2.3 per 100,000 in 2013. The rate for non-Hispanic Black females was nearly double the rate for non-Hispanic White females (4.0 compared to 2.1) and 1.6 higher than the rate of 2.5 for Hispanic females. From 1999 to 2013, cervical cancer death rates have decreased 31% for Hispanic females, 26% for non-Hispanic Black females, and 16% for non-Hispanic White females. However, this disease remains a serious public health threat, and one that demonstrates racial disparities. Incidence rates in Hispanic women and American Indian/Alaska Native women are higher than in women from other racial/ethnic groups. Despite a recent overall decline, mortality rates among African

American women remain higher than for women of any other racial/ethnic group in the United States.

Cervical cancer mortality and incidence rates also vary with socioeconomic status and geographic location, perhaps because cervical cancer screening rates vary across racial/ethnic, socioeconomic, and geographic groups (NCI, 2014). Although the overall rate of screening for cervical cancer in the United States has increased, many subpopulations are not being adequately screened. More than 60% of the women with a diagnosis of cervical carcinoma had never been screened or had not been screened within the previous 5 years of diagnosis (American College of Obstetricians and Gynecologists (2003). According to Centers for Disease Control (CDC, 2003), the report by National Breast and Cervical Cancer Early Detection Program (for 1991-2002) showed that racial/ethnic distribution of women receiving a pap smear for all years combined slightly less than half (47%) of the women were from racial/ethnic minority groups. For the most recent time period (2001–2002), the percentage from minority groups was slightly more than half (51%). Moreover, for both first and subsequent screening rounds, American Indian/Alaska Native women had the highest percentage of abnormal Pap test results (CDC, 2003).

HPV types 16, 18, 31, 33, 45, and 51 are implicated in causing cervical cancer. Recent studies have examined the association between breast and cervical cancer. Fu, Wang, Shah, Wang, Zhang, and He (2015) investigated the association of human papilloma virus type 58 with breast cancer in Shaanxi province of China. 169 cases of

breast cancer samples and 83 benign breast lesions were analyzed. The presence of HPV 58 in both normal duct epithelial cells and carcinoma *in situ* along with its presence in the cancer cells of the same specimen supports an association of HPV 58 with breast cancer (Fu et al., 2015). However, this study cannot provide information on the time to event and was not designed to analyze a correlation with BRCA gene mutations.

There is some evidence of an association between BRCA1 and cancer of the uterine body and cervix. Thompson, Easton and the Breast Cancer Linkage Consortium (2002) carried out a cohort study of 11, 847 individuals from 699 families segregating a BRCA1 mutation that was ascertained in 30 centers across Europe and North America. The purpose of the study was to evaluate the risks of other cancers besides breast in BRCA1 mutation carriers. The findings demonstrated BRCA1 mutation carriers were at a statistically significantly increased risk for several non-breast cancers, including cancer of the uterine body (RR = 2.65, P<.001) and cervix (RR = 3.72, P<.001). The study does provide evidence of association with BRCA mutations, but was limited to BRCA1.

The findings by Thompson et al. (2002) are supported by Rheim, Fisher, Bosse, Wappenschmidt and Schmutzler (2007). Rheim et al. (2007) analyzed cross sectional data from 4,405 German subjects from 409 families with BRCA1 (n=86) or BRCA2 mutations (n=53) and 270. They also included high risk BRCA1/2 negative families ascertained by the Familial Breast and Ovarian Cancer Center Cologne. The study aim was to evaluate the risk of BRCA-associated cancers using proven mutation carriers, individuals affected by breast and ovarian cancer, and their first degree relatives. They

used 921 individuals with BRCA1 (604 female; 317 male), 571 with BRCA2 (365 female; 206 male), and 2,913 who were BRCA1/2 negative (1938 female; 975 male) families that suffered from cancers other than breast and ovarian. Rheim and colleagues observed the risk for cervical cancer was significantly increased in BRCA1 and BRCA2 positive females (RR=4.59, 95% CI=2.20 to 8.44, and RR=3.69, 95% CI=1.20 to 8.61; p=<0.001) and also increased among BRCA1/2 negative families (RR=2.97, 95% CI=1.88 to 4.45) Rheim et al; (2007). These findings suggests that cervical cancer is associated with breast cancer and BRCA genes. My study further examined associations bewteen BRCA1 and BRCA2, age, ethnicity, and time to event of cervical cancer in a breast cancer population.

Time to Diagnosis of a Second Cancer

BRCA mutation status is clearly implicated in the formation of several cancers as noted in the prior sections, but there are limited data regarding time to event of these second cancers after initial diagnosis with breast cancer. In the proposed study, I examined the association between BRCA1 and BRCA2 mutation status in women with breast cancer and time to diagnosis of a second cancer, specifically pancreatic, colorectal, endometrial, or cervical cancer.

Recognizing factors that influence time to event of pancreatic cancer is crucial because symptoms of the disease may not be noted until late in the disease course (Le et al., 2011). Low survival rates are attributable to the fact that fewer than 20% of tumors are confined to the pancreas at the time of diagnosis; in most cases, the malignancy has

already progressed to the point where surgical removal is impossible (American Cancer Society, 2014).

Colorectal cancer diagnosis may also be influenced by several factors. The symptoms may present early or late in the course depending on the patient's nutrition, race, age and genetic predisposition (American Cancer Society, 2014). Patients diagnosed with rare inherited conditions, such as inflammatory bowel disease (IBD), adenomatous polyps (adenomas) (Le et al., 2011) and personal history of BRCA1/BRCA2 (Kadouri et al., 2007) may be more severely impacted. The above findings underscore the need for further investigation of factors that impact the time to event of pancreatic, colorectal, endometrial, andcervical cancer. In the following sections, I discus the pertinent literature on the variables of age, ethnicity, and gender as they relate to time to diagnosis of second cancers.

Age and Time to Diagnosis

Typically, 60 to 80 years of age is the peak incidence for developing pancreatic cancer (Mitchell et al, 2012). Pancreatic cancer is not common in persons younger than 45 years who have no predisposing risk factors, such as chronic pancreatitis and familial pancreatic cancer. After 50 years of age, the frequency of pancreatic cancers undergoes a linear increase (Dragovich, 2014). Dragovich (2014) found the average age at diagnosis was 69 years in Whites and 65 years in Blacks, while some single-institution data reported from large cancer centers (Dragovich, 2014) suggested that the average age at diagnosis in both sexes has fallen to 63 years of age. Bermejo and Hemminki (2004)

observed a twofold increased risk of pancreatic cancer in BRCA1 gene mutation carriers younger than 50 years of age. The above studies were not designed to analyze pancreatic cancer as a second cancer occurring after diagnosis of breast cancer, but do suggest that some portion of development of pancreatic cancer in a younger population could be attributable to predisposing factors such as BRCA mutations.

Some studies have analyzed age as a risk factor in diagnosing pancreatic cancer as a second cancer occurring after breast cancer diagnosis. Mocci et al. (2013) in a retrospective cohort study analysis observed that the women diagnosed with a BRCA mutation related breast cancer before 50 years of age were at a higher risk for developing pancreatic cancer as second cancer. This finding is supported by an earlier study by Brose et al. (2002) that found observed threefold risk of pancreatic cancer among BRCA1 mutation carriers with breast cancer in comparison with the SEER Program population-based estimates.

The risk of colon cancer has also been found to increase in individuals below 50 years of age who have BRCA germline mutations (Phelan et al., 2014; Suchy et al., 2010; Ford et al., 1994). Phelan et al. found an increased risk of colorectal cancer among female carriers of BRCA1 gene mutation who were below 50 years of age, but not in older women or individuals with BRCA2 mutations (Phelan et al., 2014). Suchy et al. (2010) observed the mean age at onset of primary colon cancer in *BRCA* carriers was 7 years younger than in non-carriers (57.0 years vs. 64.0). Ford et al. (1994) found primary ovarian cancers occurred in women with a previous breast cancer, with an estimated

cumulative risk of ovarian cancer of 44% by age 70. A higher risk of second cancers, including colon cancer, were also noted in individuals with breast or ovarian cancer and their first-degree relatives compared with expected national incidence rates.

Although data is limited, the above findings imply that BRCA mutations have the potential to be a risk factor for development of second cancers after diagnosis with breast cancer, particularly for younger individuals.

Beiner et al. (2007) conducted a prospective cohort study that examined the risk of endometrial cancer in women with BRCA1 *and* BRCA2 mutations. An international registry was used to identify women subjects with known BRCA1 or BRCA2 mutations, aged 45 to 70 and they were followed prospectively. The study involved 857 participants who completed a baseline questionnaire and one or more follow-up questionnaires. Study subjects were followed until diagnosis of endometrial cancer, ovarian cancer, death or the date of completion of the last questionnaire. The expected number of endometrial cancers was calculated using age and country-specific incidence rates (Beiner et al., 2007). The study findings indicated six women were diagnosed with endometrial cancer, compared to 1.13 cancers expected after follow-up (SIR = 5.3, $p = 0.0011$). Four of these six patients used tamoxifen in the past. The risk among women who were never exposed to tamoxifen treatment was not significantly elevated (SIR = 2.7, $p = 0.17$), but among the 226 participants who had used tamoxifen (220 as treatment and six for the primary prevention of breast cancer) the relative risk for endometrial cancer was 11.6 ($p = 0.0004$) (Beiner et al., 2007). The above study demonstrated an increased risk of endometrial

cancer with age among BRCA carriers who had a previous breast cancer and were treated with tamoxifen.

Little is known about the age at diagnosis of cervical cancer and association with BRCA mutation (Brose et al., 2002). Brose et al. (2002) evaluated cancer risk estimates by age 70 for BRCA1 mutation carriers and indicated several cancer risk estimates for BRCA1 mutation carriers. The cumulative age-adjusted lifetime second cervical cancer risk in BRCA1 mutation carriers for 95% CI was 0.3 (0.3 to 0.8) with a corresponding population risk of 0.8%.

Ethnicity and Time to Diagnosis

There are some data on ethnicity and risk of second cancers, but few have looked specifically at time to diagnosis of second cancers. Lee et al. (2008) found the peak incidence for a second cancer in Taiwanese women diagnosed with breast cancer at a young age was among women in their 40s. Approximately 2% developed a non-breast second primary cancer, with an average survival time of 2.87 years after the second cancer diagnosis.

Other studies done in various populations have provided data correlating BRCA mutations with the risk of developing second cancers, but without analyzing the time to diagnosis. A study among breast cancer families in Iceland found that BRCA was responsible for a small proportion of second cancers, including endometrium, colon, lung, prostate, stomach and thyroid cancer (Johanannesdottir et al., 1996). Al-Mulla et al. (2009) observed a significant association in United Kingdom families with breast

and/or ovarian cancer and BRCA1 or BRCA2 mutation and the occurrence of a second cancer including vaginal, colon, prostate, and pancreatic cancers (Al-Mulla et al., 2009).

There is indication that Ashkenazi ethnicity could be neutral or perhaps even protective against the risk of developing colorectal cancer after diagnosis with a BRCA mutation, perhaps relating to the particular BRCA mutations present in this population (Niell et al., 2004). Niell et al. genotyped a northern Israeli population for the BRCA1 187delAG, BRCA1 5385insC, and BRCA2 6174delT founder mutations. A family history of breast cancer in a female relative was not associated with an increased risk of colorectal cancer, even after adjustment for the presence of a BRCA founder mutation. Ashkenazi BRCA founder mutations may not confer a strong high risk of colorectal cancer and do not seem to be risk factor for colorectal cancer in that population (Niell et al., 2004). This study did not look at colon cancer as a second cancer after breast cancer, but provides some useful information about the role of ethnicity, which may relate to the type of BRCA mutation carried. These findings are consistent with other studies on Ashkenazi's Jewish population finding no association between BRCA gene mutations and colon cancer (Kadouri et al., 2007; Drucker, Stackievitz, Shpitz, & Yarkoni, 2000). However, this suggests more data is necessary for other ethnic groups, which may be at a higher risk.

There is some evidence for increased risk of pancreatic cancer in BRCA1 and BRCA2 mutation carriers in European and North American groups (Thompson & Easton, 2002). Thompson and Easton found that BRCA1 mutations may confer small but

increased risks of other abdominal cancers in women and increased risks of pancreatic cancer in men and women (Thompson & Easton, 2002).

Few studies have investigated ethnicity as a risk factor of endometrial cancer diagnosis among women with BRCA mutations (Setiawan, et al., 2006; Ofer et al., 2000; La Vecchia et al., 1984). Ofer et al. (2000) carried out a population study among the Jewish population with the study aim of determining the possible effects and incidence of BRCA1 and BRCA2 germline mutations in uterine serous papillary carcinoma (a subtype of endometrial carcinoma). Ofer et al. (2000) screened DNA from 12 women with uterine serous papillary carcinoma for BRCA1 and BRCA2 germline mutations common in the Jewish population (BRCA1–185delAG and 5382insC, BRCA2–6174delT). In women subjects with germline mutations, tumor DNA was screened for loss of heterozygosity at the appropriate loci. They found nine women were of Jewish Ashkenazi origin and three were non-Ashkenazi. Two of nine Ashkenazi women were carriers of germline mutations: one 185delAG mutation and one 5382insC mutation. Five women had histories of breast carcinoma before diagnosis of uterine serous papillary carcinoma. Family histories of seven women had at least one first-degree relative with malignant disease. Of those, four had at least one first-degree relative with breast, ovarian, or colon carcinoma. Both carriers had strong family histories of breast-ovarian carcinoma. Loss of heterozygosity analysis found loss of the wild-type BRCA1 allele in the primary uterine tumors. BRCA1 germline mutations were observed in two of nine of the women in this series. The loss of heterozygosity in the tumor tissue of the carriers,

coupled with the high frequency of family and patient histories of breast or ovarian malignancies, suggest that uterine serous papillary carcinoma might be a manifestation of familial breast-ovarian cancer (Ofer et al., 2000). The above study supports other findings (Shu et al., 2014; Thompson et al., 2002; Levine et al., 2001) that ethnicity is a risk factor for endometrial cancer among populations with BRCA gene mutations.

Thompson et al. (2002) found that BRCA1 mutation carriers were at a statistically significantly increased risk for several non-breast cancers, including cancer of the uterine body (RR = 2.65, P<.001) and cervix (RR = 3.72, P<.001). The study does provide evidence of association with BRCA mutations, but was limited to BRCA1 (Thompson et al., 2002). However, this study did not specifically aim to look at second primary cancers. My study will further examine the association between ethnicity as a risk factor for the time to diagnosis of second primary pancreatic, colorectal, endometrial, or cervical cancer in the study population

Gender and Time to Diagnosis

Male gender may be a risk factor for developing second cancers in those with BRCA1 and BRCA2 related breast cancer (Hemminki et al., 2005). Some risks are necessarily gender specific. For example, the risk for prostate cancer is associated only with the male gender (Hemminki et al., 2005), while the risk for ovarian, endometrial, and cervical cancer found in other studies is associated only with females (Shu et al., 2014; Evans et al., 2009; Rheim et al., 2007). However, breast cancer is not limited to females and men with BRCA1 mutations are at increased risk of cancers of the breast

(Agalliu et al., 2007). Evidence supporting a gender difference for increased susceptibility to colon cancer is limited (Brose et al., 2013; Kadouri et al., 2007).

There are some data that women have a greater lifetime risk of cancer with mutations of the BRCA1 gene, while BRCA2 conveys a greater risk for men. The spectrum of cancers is wider for BRCA2, and Liede et al. (2004) reported that the overall cancer risk for male BRCA2 carriers was higher than the risk for female carriers (Liede, Karlan, & Narod, 2004). Liede et al. (2004) found the relative risk to male BRCA2 mutation carriers was highest before 65 years of age, mostly attributable to breast, prostate, and pancreatic cancers. BRCA2 mutation carriers are also at risk of stomach cancer and melanoma of the skin and eye (Liede et al., 2004). A limitation is that the Liede study was not designed to study second cancers after diagnosis of BRCA related cancer.

Additional research into gender differences for BRCA mutation carriers is needed to ascertain the scope and magnitude of excess cancer risk in BRCA carriers. By critically examining the non-modifiable risk factors that may contribute to BRCA1/BRCA2 mutation related breast cancer and second cancers, I will provide data to help focus screening and risk reduction mechanisms. The following sections describe the methods of BRCA mutation detection, treatment options for breast, colorectal, and pancreatic cancer, and prognoses.

Detection, Treatment, and Prognoses

BRCA Mutation Detection

Currently, there are several available genetic detection methods used for detecting BRCA1 and BRCA2 gene mutation status. Tests can ascertain multiple mutations in both genes using a blood or saliva sample for DNA. Due to the relative rareness of the deleterious BRCA1 and BRCA2 gene mutations in the general population, it is generally recommended that mutation testing should be done only in patients with family history suggestive of the possible presence of a deleterious mutation in BRCA1 or BRCA2. The United States Preventive Services Task Force (2013) has provided a recommendation encouraging women whose close relatives are diagnosed with breast, ovarian, fallopian tube, or peritoneal cancer to be evaluated to ascertain if they have a family history that predispose them to an increased risk of a deleterious mutation in one of these genes.

There are some screening tools to assess family history factors that are associated with an increased likelihood of having a harmful mutation in BRCA1 or BRCA*2*. These include breast cancer diagnosed before age 50 years, cancer in both breasts, having both breast and ovarian cancers, having multiple breast cancers, two or more primary types of BRCA1- or BRCA2-related cancers in a single family member, cases of male breast cancer, and Ashkenazi Jewish ethnicity (United States Preventive Services Task Force, 2013).

While screening can provide patients with some clarity regarding their risks, these individuals may then need to decide what to do with the information. The options at this time are fairly limited for patients diagnosed with BRCA1 or BRCA2 gene mutations to manage their risk of getting cancer, and include an enhanced screening method, the use of

prophylactic (risk-reducing) surgery, and the application of chemoprevention techniques (NCI, 2014). These options are discussed in further detail below.

The enhanced screening option is recommended for women with a positive BRCA1 or BRCA2 test result at a young age. Women who carry the deleterious BRCA1 or BRCA2 are encouraged to undergo clinical breast examination and a mammogram every year beginning at age 25 to 35 years (Burke et al., 1997). This option increases the chance of early detection of breast cancer and the likelihood of a better prognosis during treatment.

MRI and mammography are widely used breast cancer detection tools. The use of MRI in breast cancer screening may be more sensitive than mammography (Kriege et al., 2004), especially in high risk women who are BRCA1 or BRCA2 positive (Warner et al., 2004). However, mammography can detect some breast cancers that are not detected by MRI (Obdeijn, et al., 2010), and MRI may be less specific (generating false positive outcomes) than mammography.

It has not been fully elucidated if there is any benefit of screening for breast and other cancers in men that have positive BRCA1 or BRCA2 mutation diagnosis, but it has been suggested that men with positive BRCA1 and BRCA2 mutations should undergo prostate cancer testing and regular mammography (NCI, 2014).

Breast Cancer Treatment and Prognosis

The array of breast cancer treatment options for some patients may involve aggressive surgery, chemotherapy, and radiotherapy, whereas others may receive only the

primary tumor surgical resection. To ascertain the best option for each patient, a risk prognostic, predictive data, as well as profile composing of clinical data is normally gathered (Singletary, 2004). Some prognostic markers such as lymph node status, tumor size, histologic subtype, proliferation rate, and hormone receptors are often used to ascertain a population-based estimate of the absolute risk of recurrence and/or death. Due to the relationship between prognostic factors and natural disease history, it is often suggested that these data are seen as treatment independent (Singletary et al., 2004). On the other hand, Singletary and Colleagues presented that predictive markers are usually utilized when identifying patients who will benefit, or not benefit, from a particular therapeutic regimen. Predictive markers are viewed as treatment associated. Some of these markers include the estrogen receptor (used to identify patients who will possibly benefit from hormonal therapy (Singletary et al., 2004).

Due to the involvement of BRCA1 and BRCA2 genes in DNA repair, a deleterious mutation in either of these genes may be more sensitive to anticancer agents that act by damaging DNA, such as cisplatin (NCI, 2014). According NCI (2014), data from preclinical investigation on drugs associated with blocking repair of DNA damage have been found to inhibit the growth of cancer cells that have BRCA1 or BRCA2 mutations. These drugs have likewise demonstrated some activity in cancer patients who carry BRCA1 or BRCA2 mutation breast cancer patients (NCI, 2014).

Prophylactic surgery remains an option for women who carry BRCA1 and BRCA2 mutations. This is usually done by surgically removing as much “tissue at risk”

as possible with the option of bilateral mastectomy (removal of both breasts) (NCI, 2012). Chemoprevention has been used extensively in delaying the recurrence and reducing risk of cancer. Chemoprevention therapy involves the use of drugs, vitamins and other agents in cancer treatment (NCI, 2014). Currently, the Food and Drug Administration (FDA) has approved two drugs with the aim of reducing the risk of breast cancer in women with increased predisposing risk factor, tamoxifen and raloxifen. The effect of these drugs in patients with the deleterious BRCA1 and BRCA2 mutations has not been well elucidated (NCI, 2014) and it remains unclear whether they could reduce the incidence of colon or pancreatic cancers among BRCA mutation carriers who have been diagnosed with breast cancer. Tamoxifen may have the potential to help in lowering the risk of cancer of the breast in BRCA1 and BRCA2 mutation carriers (King et al., 2001) and has been associated with lowering risk of cancer in the opposite breast among women with a diagnosis of breast cancer (Phillips et al., 2013).

Pancreatic Cancer Detection, Treatment, and Prognosis

Pancreatic cancer onset is often very subtle. In most cases, it has metastasized prior to detection; resulting in poor prognosis (Le et al., 2011). Pancreatic carcinoma of the head of the pancreas is mostly characterized with painless obstructive jaundice. Patients with this sign may come to medical attention before their tumor grows large enough to cause abdominal pain. These patients usually notice a darkening of their urine and lightening of their stools before they or their families notice the change in skin pigmentation (Dragovich, 2014). Physicians can normally recognize clinical jaundice by

laboratory assay of total bilirubin, which patients and families may not notice until clinical jaundice is apparent. Urine darkening, stool changes, and pruritus are often noticed by patients before clinical jaundice (Dragovich, 2014).

Surgical therapy has always been the mainstay of the primary mode of treatment for pancreatic cancer. It has also been observed that the use of chemotherapy and/or radiation therapy plays an important role in an adjuvant or neoadjuvant environment, and in the treatment of patients with unresectable disease (Dragovich, 2014).

There are several innovations for detection and pancreatic cancer treatment. NCI (2014) reported on the development of a laparoscopic technique that uses fluorescent light to improve pancreatic cancer staging and treatment, the Early Detection Research Network (EDRN) to enhance cancer detection and risk assessment, and investigation of stem cell biomarkers for early detection of pancreatic cancer.

Cancer of the pancreas is very aggressive and often associated with poor prognosis (Le et al., 2011). The overall average survival time for patients range between 2 months and 6 months (Dragovich, 2014). The American Cancer Society (American Cancer Society, 2014) recently suggested that the relative 1-year survival rate for patients with pancreatic cancer is only 24%, and the overall 5-year survival rate is 5%, having increased from the 3% rate calculated between 1975 and 1977. Notwithstanding, patients with neuroendocrine and cystic neoplasms of the pancreas, such as mucinous cystadenocarcinomas or intraductal papillary mucinous neoplasms [IPMN], have demonstrated better survival rates than do patients with pancreatic adenocarcinoma.

A 5-year survival in pancreatic cancer is no guarantee of cure; patients who survive for 5 years after successful surgery may still succumb to death due to recurrent disease years after the 5-year survival point. The occasional patient with metastatic disease or locally advanced disease who survives beyond 2-3 years may die of complications of local spread, such as bleeding esophageal varices (Dragovich, 2014).

Colon Cancer Detection, Treatment, and Prognosis

Due to the increased emphasis on screening practices, colon cancer is now often detected before it starts to cause symptoms. Currently, it is suggested patients 50 years and older undergo a screening test with stool occult blood test and colonoscopy (Le et al., 2011), or a multimarker test for stool DNA (sDNA) (Mayo, 2014). The tumor may also be detected as a lesion seen on barium enema x-ray (Le et al., 2011). In advanced colon cancer cases, common clinical presentations include iron-deficiency anemia, rectal bleeding, abdominal pain, change in bowel habits, and intestinal obstruction or perforation. Right-sided lesions are more likely to bleed and cause diarrhea while left-sided tumors are usually detected later and may present as bowel obstruction (Dragovich, 2014).

There are several treatment options for colon cancer. These include surgery, chemotherapy, and biologic agents (Dragovich, 2014). Surgery has been the major option for curative modality for localized colon cancer (stage I-III). Surgical resection potentially provides the only curative option for patients with limited metastatic disease in liver and/or lung (stage IV disease), but the proper use of elective colon resections in

non-obstructed patients with stage IV disease is a source of continuing debate (Dragovich, 2014).

In the United States, the approximate 5-year survival rate for colorectal cancer patients (all stages included) is 65 % (Dragovich, 2014). Survival is noted to be inversely related to stage: approximate 5-year survival rates are 95% for patients with stage I disease, 60% for those with stage III disease, and 10% for those with stage IV (metastatic) disease (Dragovich, 2014). Chua Saxena, Chu, Zhao, & Morris (2011) in their investigation observed that approximately one in every three patients who undergo resection for colorectal liver metastases become actual 5-year survivors. Out of those, about half get to 10 years and are cured of colorectal liver metastases. Similarly, Fong, Fortner, Sun, Brennan, & Blumgart (1999) conducted a multivariate analysis that involved 1001 patients who underwent potentially curative resection of liver metastases. Fong and colleagues observed five factors as independent predictors of worse outcome. These include Size greater than 5 cm, disease-free interval of less than a year, more than one tumor Primary lymph node positivity, and Carcinoembryonic antigen (CEA) level greater than 200 ng/mL (Fong et al., 1999).

Endometrial Cancer Detection, Treatment and Prognosis

Predisposing risk factors for endometrial cancer include age (postmenopausal, 50 to 70 years), estrogen therapy without progesterone, obesity, family history of uterine, colon, or ovarian cancer, difficulty getting pregnant, fewer than five periods in a year before starting menopause, and previous treatment of breast cancer with tamoxifen

(CDC, 2014). Signs and symptoms of endometrial cancer include abnormal vaginal bleeding not related to menstruation (observed in 80% of patients), difficulty or painful urination, pain during intercourse and pain in the pelvic area (NCI, 2015). Palpation of abdomen and pelvic region may detect endometrial cancer associated mass (Le et al., 2006). No blood studies can confirm the diagnosis of endometrial carcinoma. Pap test is not often useful because endometrial cancer cells start inside the uterus and are not usually observed in the results. Confirmatory diagnosis may require that a sample of endometrial tissue be removed by endometrial biopsy and dilation curettage and checked under a microscope to look for cancer cells. A physical exam and history, transvaginal ultrasound exam, and CAT scan are also useful tools for endometrial cancer detection (NCI, 2015).

Endometrial cancer is treatable if detected early before it spreads. Treatment of endometrial cancer depends on type and the extent of the spread and may involve surgical techniques to remove cancer tissue, lymph node dissection, progesterone therapy and radiotherapy. Chemotherapy is often used in treatment of advanced cases.

Endometrial cancer is curable and usually has good prognosis. The overall 20-year survival rate for all forms of endometrial carcinoma is about 80%, in comparison to 62% for clear cell and 53% for papillary carcinomas (Colombo et al., 2013). The chance of patient recovery may depend on cancer stage (if located only in the endometrium, involves the whole uterus or has metastasized to other body regions), if the cancer cells

are affected by progesterone, and the appearance of the cancer cells under a microscope (NCI, 2015).

Cervical Cancer Detection, Treatment and Prognosis

A common early symptom of cervical cancer is abnormal vaginal bleeding. Patients may also have history of metrorrhagia, postcoital spotting, discharge (bloody or purulent, odorous, nonpruritic). In some cases, it may be asymptomatic (Le, Bhushan, & Skapik, 2006). Most cases are observed in premenopausal and women greater than 40 years of age. Early stage diagnosis of cervical cancer increases the chance of a better prognosis. Detection of treatable pre-cancer in sexually active women can be enhanced by regular cervical screening tests, such as Pap smear (Le et al., 2006). Usually during each test, some cells are removed from the surface of the neck of the cervix. These cells are sent to the laboratory to be examined under a microscope. Normal cells are observed in most cells, while abnormal (dyskaryotic) cells are noticed in some cases. The test may also be helpful in detecting the human papillomavirus (HPV) which is a type of wart virus often implicated in the development of cervical cancer (National Cancer Institute, 2014). Pelvic examination for lumps or abnormal areas during exam of the vagina, cervix, uterus, fallopian tubes, ovaries, and rectum is often used (NCI, 2014).

Treatment options are often based on the stage of the cancer, type of cervical cancer, desire to have children, and age (NCI, 2014). Early treatment stage may involve chemo-radiation, radical hysterectomy, and lymphadenectomy. Advanced treatments of cervical cancer include irradiation and chemotherapy (Le et al., 2006).

Cervical cancer can be cured if detected early and the prognosis is best in patients who are diagnosed when cervical cancer is confined to the neck of the cervix and has not spread. According to the 1988 Bethesda System for reporting cervical/vaginal cytological diagnoses (1989), the prognosis for patients with cervical cancer is markedly affected by the extent of disease at the time of diagnosis. Greater than 90% of cervical cancer cases can be detected early through the use of the Pap test and HPV testing. Pap and HPV testing are not performed on approximately 33% of eligible women, which results in a higher-than-expected death rate.

Grading and Staging

According to Mitchell et al. (2012), the grade and stage of malignant neoplasms provide a semi-quantitative estimate of the clinical gravity of a tumor: Grading is based on the degree of differentiation and the number of mitoses within the tumor. Cancers are classified as grades I to IV with increasing anaplasia. In general, higher-grade tumors are more aggressive than lower grade tumors. Grading is assumed imperfect because different parts of the same tumor may display different degrees of differentiation and the grade of the tumor may change as the tumor grows (Mitchell et al., 2012).

Staging is founded on the anatomic extent of the tumor. Relevant to staging are the size of the primary tumor and the extent of local and distant spread. Two methods of staging are currently in use: The TNM (tumor, node, metastases) and the AJC (American Joint Committee) systems. Both systems assign to a higher stage those tumors that are larger, locally invasive, and metastatic (Mitchell et al., 2012). Histologic grading and

clinical staging are valuable for prognostication and for planning therapy, although staging has proved to be of greater clinical value (Le et al., 2011). This underscores the need for further study on the various risk factors that could play significant role in diagnosis and prognosis of various cancers that may have the potential to be malignant. Therefore, my study will examine the time to diagnosis of second primary pancreatic, colorectal, endometrial, and cervical and cancer among women with breast cancer as well as associations with patient age, gender, race, and ethnicity. The following section explores other relevant studies that have used similar methodologies and provides support for my chosen methodology.

Studies Using BCFR

The BCFR database is recognized as a standard data set for conducting quality research. Quality assurance remains one of the top priorities of all the six participating sites (BCFR, 2013). Since the inception of BCFR in 1996, several studies have been conducted with the data sets collected from different BCFR database sites across the United States (Gaudet et al., 2010), Canada and Australia (Dite et al., 2010). These studies included both population-based genetic investigations using focus groups and telephone interviews to ascertain knowledge levels about screening options (Lewis, Frost, & Venne, 2009) as well as clinic-based studies (Mclure et al., 2010). The following sections describe the most relevant studies that have used this data set and how the proposed study will add to this knowledge.

Dite et al. (2010) carried out a cohort study with BCFR data set that involved 2,208 parents and siblings of 504 unselected population-based Caucasian women with breast cancer who were diagnosed before 35 years of age. The women were from Australia, Canada, and United States, carrying mutations in BRCA1, BRCA2, or both genes. Dite and colleagues employed cancer-specific standardized incidence ratios (SIRs) which were estimated by comparing the number of affected relatives (50% verified overall) with that expected based on incidences specific for country, sex, age and year of birth (Dite et al., 2010). The investigators found that first-degree relatives of women that had very early-onset breast cancer were at increased risk of other cancers, such as lung, ovarian, urinary and prostate cancer. The observed increased risks were mostly evident in younger women and women with at least one affected relative with early age diagnosis (Dite et al., 2010). There are several limitations to this study. Dite and colleagues only studied women from one ethnic group (Caucasian). They also did not explore other cancers such as pancreatic and colorectal that have been found in other studies to have association with BRCA1 and BRCA2 (Mocci et al., 2013; Brose et al., 2002). The study was not designed to study time to diagnosis of second cancers. My study will go beyond this study to examine ethnicity, gender, and age, and time to diagnosis of pancreatic and/or colon cancer among women with breast cancer.

Several other epidemiologic investigations on breast, pancreatic, and colon cancers have been done using BCFR data (Mocci, et al., 2013; Kadouri et al., 2009; Niell et al., 2004). Mocci et al. (2013) analyzed high-risk breast cancer families from six BCFR

sites in the United States, Canada, and Australia for the risk of pancreatic cancer in families with germline BRCA1 or BRCA2 mutation related breast cancer. They used one-way ANOVA to determine the age mean difference in individuals diagnosed with pancreatic cancer. They also employed the survival analysis technique to ascertain the time in years from birth to diagnosis of pancreatic cancer, death, or last contact (Mocci et al., 2013). Mocci et al. found germ-line BRCA1 carriers were at increased risk of pancreatic cancer. However, the study was not designed to look at second cancers in breast cancer patients and was limited to BRCA1 carriers and associated risk of pancreatic cancer in breast cancer families. My study will go further to use Cox Proportional Hazards to model the relationships between the independent and dependent variables among three cohorts and survival analysis will ascertain the probability of the incidence proportion.

My study will use BCFR data to explore age at diagnosis with breast cancer, ethnicity, and gender and the relationship with time to diagnosis of a second pancreatic colorectal, endometrial and cervical cancer. To date, no other study has been published that has used BCFR data to specifically determine all of these variables. The literature reviewed for this chapter supports the use of the BCFR data set and Cox Proportional Hazard to model the relationships between the independent and dependent variable among three cohorts and survival analysis to ascertain the probability of the incidence proportion (Mocci et al., 2013). There are other genes besides BRCA that increase the risk of colon cancer in susceptible individuals (Meijer-Heijboer et al., 2003) which are

outside the scope of this study. Any limitations to interpretations resulting from this scope will be discussed further in Chapter 5.

Summary

BRCA1 and BRCA2 related breast cancer is a genetic disorder in which the control of cell proliferation is lost (Nussbaum et al., 2007). The fundamental mechanism pertaining to all cancers is a genetic mutation, either in the germline or more frequently, in the somatic cells (Nussbaum et al., 2007). There is much yet to be learned about the genetic process of the origin of cancer and the factors that may trigger a malignancy. This chapter reviewed the current state of knowledge for the variables that will be used in the proposed study, including age, ethnicity, gender as risk factors for second cancers among a BRCA-related breast cancer population.

Age is a risk factor for both primary breast cancer (Mitchell et al., 2012) and second primary cancers (Lee et al., 2008). Several studies reported that women with BRCA1 and BRCA2 germ-line mutations were at a higher risk for being diagnosed with second cancer before 50 years of age (Mocci et al., 2013: Brose et al., 2002). Mocci et al. (2013) found that the women diagnosed with a BRCA mutation related breast cancer before 50 years of age were at increased risk of pancreatic cancer. Brose et al. (2002) observed that by 70 years of age, the risk among BRCA1 carriers of being diagnosed with ovarian cancer was 40.7%.

Data on ethnicity as a risk factor for BRCA gene mutations and second primary cancers were documented for several ethnic groups, including Ashkenazi Jews (Niell et

al., 2004), United States Caucasians (Mocci et al., 2013), Australians and Canadians (Dite et al., 2010). Taiwanese (Lee et al., 2008), and Europeans (Thompson & Easton, 2002). Niell et al. (2004) found Ashkenazi ethnicity may be protective against risk of developing colorectal cancer after diagnosis with a BRCA gene mutation, suggesting the type of mutation is relevant. However, Mocci et al. (2013) observed families of Caucasian breast cancer BRCA1 gene mutation carriers were at increased risk of pancreatic cancer. Dite and colleagues also noted that first-degree relatives of Australian and Canadian women that had very early-onset breast cancer were at increased risk of other cancers, such as lung, ovarian, urinary and prostate cancer (Dite et al., 2010). Lee et al. (2010) found the peak incidence for age at diagnosis of second cancer among Taiwanese women was in their 40s, with poor prognosis after the second cancer diagnosis (Lee et al., 2008). Thompson and Easton found that BRCA1 gene mutations conferred small but increased risks of other abdominal cancers in European women and increased risks of pancreatic cancer in men and women (Thompson & Easton, 2002). There is a need for additional studies in various ethnic and racial groups, as varying founder mutations may confer different risks.

Gender as a risk factor has been well studied in both primary breast cancer (Mitchell et al., 2012) and second primary cancer (Phelan et al., 2014; Lee et al., 2008; Hemminki et al., 2005). There are some data suggesting that women may have a greater life time risk of cancer with BRCA1 gene mutations, while BRCA2 gene mutations conveys greater risk for men (Liede, Karla, & Narod, 2004). Liede et al. (2004) found the

relative risk to male BRCA2 gene mutation carriers was highest before 65 years of age, mostly attributable to breast, prostate, and pancreatic cancers. The increased risks for pancreatic or colon cancer in patients with BRCA1 or BRCA2 gene mutations have been observed in both female (Kadouri et al., 2007) and male (Hemminki et al., 2005) subjects, while BRCA1 conveys a higher risk of ovarian cancer in women (Le et al; 2011). More data is needed on the interplay between gender and other study variables with time to event of second primary, pancreatic and colon cancers.

The option of early detection of breast cancer provides the likelihood of a better prognosis during treatment. Women who carry the deleterious BRCA1 or BRCA2 gene mutations are encouraged to undergo clinical breast examination and a mammogram every year beginning at age 25 to 35 years (Burke et al., 1997). The prognosis of second primary cancers, such as pancreatic, colorectal, endometrial, and cervical cancers may vary depending on age of diagnosis, ethnicity and gender. Pancreatic cancer onset is often very subtle. In most cases, it has metastasized prior to detection; resulting in poor prognosis (Le et al., 2011). The overall average survival time for patients range between 2 months and 6 months (Dragovich, 2014). In the United States, the approximate 5-year survival rate for colorectal cancer patients (all stages included) is 65 % (Dragovich, 2014). Survival is noted to be inversely related to stage: approximate 5-year survival rates are 95% for patients with stage I disease, 60% for those with stage III disease, and 10% for those with stage IV (metastatic) disease (Dragovich, 2014). Predictive markers have been useful in treatment options (Singletary et al., 2004). The association between

germline mutations in BRCA genes and the risk of endometrial cancer remains unclear, but several case reports of endometrial carcinoma in women with a *BRCA* gene mutation exist (Oh et al., 2015; Levine et al., 2001). Age-adjusted data based on 2008-2012 cases and deaths, there were 25.1 per 100,000 new cases of endometrial cancer in the United States per year; while the number of deaths was 4.4 per 100,000 women per year. 2012 prevalence data from SEER (2015) estimated that 621,612 women were living with endometrial cancer in the United States. Since, 1999 to 2013, cervical cancer death rates have decreased 31% for Hispanic females, 26% for non-Hispanic Black females, and 16% for non-Hispanic White females. However, this disease remains a serious public health threat, and one that demonstrates racial disparities

Due to the cancer risks associated with BRCA gene mutations, and the poorer prognosis for individuals with second cancers, particularly for pancreatic, colorectal, endometrial, cervical, kidney, thyroid, and bladder cancer, understanding the risk factors associated with time to diagnosis of second cancers after breast cancer in this population is crucial. The results of this study will aid clinicians in determining appropriate screening and timely treatment and interventions to reduce mortality and improve health outcomes.

Chapter 3 discussed the research design and rationale, population, sampling and sampling procedures, and a power analysis and sample size estimate. Instrumentation and materials, data collection and analysis, and examined the independent variables,

dependent variables, as well as study questions were also included. Quality assurance and protection of human subjects concludes the chapter.

Chapter 3: Research Method

The purpose of this study was to test the relationship of gender, ethnicity, and age of diagnosis of breast cancer to time to diagnosis for two second primary cancers, pancreatic and colon cancer. Specifically, I investigated these associations within the framework of time-to-event analysis. In this chapter, I present the research design and rationale in which I discuss the study research questions and examine study research designs in relationship to the research questions. I also address constraints related to research choice and consistency of research choice with the state of knowledge in the field. In the study population section, I describe the population under study and target population size estimates. I also include information on the sample and sampling procedures that I applied to this study. This study was a secondary data analysis, and no treatment of any kind was used during this study. In the instrumentation section, I detail the data collection methods, and I discuss the reliability, validity, and the type of data that were assessed using the BCFR data set. In the data analysis section, I explain the use of SPSS software and statistical tests such as the CPH and logistic regression for analysis of both the independent and dependent study variables. The last session includes the protection of study participants and information regarding how BCFR sites ensured that all study subjects' data are kept confidential and the role of Walden University IRB to ensure that ethical standards are not violated.

Research Design and Rationale

The research questions for this study were as follows:

RQ1: Is there a relationship between BRCA mutation status and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among women with breast cancer?

RQ2: Is there a relationship between ethnicity and age status and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among women with BRCA-related breast cancer?

RQ2a: Is there a relationship between ethnicity and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among women with BRCA-related breast cancer?

RQ2b: Is there a relationship between age status and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among women with BRCA-related breast cancer?

RQ3: Is there a relationship between gender and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among men and women diagnosed with BRCA-related breast cancer?

H_0: There is no relationship between gender and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among men and women diagnosed with BRCA-related breast cancer.

H_a: There is a relationship between gender and time to diagnosis of second cancers, pancreatic, colorectal, endometrial, or cervical, among men and women diagnosed with BRCA-related breast cancer.

The study was a quantitative cohort design using secondary data. I used three cohorts to answer the research questions. These are presented in Table 1.

Table 1

Research Questions, Independent Variables, and Cohort

Research Question	Independent Variable	Cohort
RQ 1	*BRCA* mutation status among women with breast cancer	Women with a diagnosis of Breast Cancer with and without *BRCA* gene mutations
RQ 2	Ethnicity and Age	Women with *BRCA* related Breast Cancer
RQ 3	Gender	Men and Women with *BRCA* related Breast Cancer

Note. In each case, the dependent variable is the diagnosis of second primary cancer, pancreatic, colorectal, endometrial, and cervical cancer

The first cohort consisted of women with a diagnosis of breast cancer, with and without BRCA gene mutations. In this cohort, I compared time to diagnosis of second cancers of the, colon/rectum, endometrium, cervix, kidney, thyroid, and bladder. The second cohort contained only women with a diagnosis of BRCA-related breast cancer. I analyzed the relationship of the risk factors of ethnicity and age at initial diagnosis of breast cancer as the independent variables, to time to diagnosis of second colorectal, endometrial, cervical, kidney, thyroid, or bladder cancers as the dependent variables. The third cohort included men and women with a diagnosis of BRCA-related breast cancer,

with gender as the independent variable. In the third cohort, I planned initially to compare time to diagnosis of second cancers of the colorectal, endometrial, cervical, kidney, thyroid, and bladder for women.

As a result of inclusion of endometrial, cervical, kidney, thyroid, and bladder cancer with the intention of increasing the study power, the composite endpoint-based analysis was employed. This was done using the CPH model. The hazard ratio generated was measured in the association in this case. The known BRCA mutation status of all breast cancer cases served as a strata variable. Event was defined = 1 if there was pancreatic or colorectal or endometrial, or cervical cancer after diagnosis with breast cancer; else event = 0. A composite endpoint (outcome) consists of two or more component outcomes (in the above case, pancreatic, colorectal, endometrial and cervical cancer). Patients who have experienced any one of the events specified by the components are considered to have experienced the composite outcome (Ferreira-Gonzalez et al., 2007). The benefits of the application of a composite endpoint are that it increases statistical efficiency and power due to higher event rates, which reduces sample size need; it helps researchers avoid an arbitrary choice between several important outcomes that refer to the same disease process; and it is a means of evaluating the effectiveness of a patient-reported outcome that addresses more than one aspect of the patient's health status (Ferreira-Gonzalez et al., 2007; Ross, 2007).

I anticipated no time or resource constraints for this study design choice. However, I did experience some delay in getting approvals processed by the NCI -

Columbia University Breast Cancer Family Registry (BCFR) Data Center. The study was a quantitative cohort design that used a secondary dataset collected over many years by various BCFR sites. These data are free and easily accessible to researchers in collaboration with the BCFR. After I submitted a collaboration agreement application form, the application was assessed, and the research was approved. A BCFR liaison contact (a preceptor and expert in the area of interest) was assigned to work with me during the data collection and analysis phases of the study. It takes approximately 1 month to receive a BCFR approval, from the time of application to the assigning of a BCFR liaison contact (BCFR, 2013).

I chose a quantitative cohort study design due to its use in similar studies (Houser, 2012). The quantitative cohort study design is useful in determining relationships between a risk and an outcome, with causality inferred based on varying criteria. The relationship between breast cancer risk factors and disease cannot be tested with a true experimental design because it is not ethical to expose individuals to risk factors they would otherwise not experience. These variables must be studied as they naturally occur. This quantitative study design does not allow me to control many extraneous, modifiable variables; this was a limitation to this study

Study Population

I used secondary data from the BCFR. The BCFR contains data on the general population as well as clinic-based data. The BCFR collects health data and biospecimens from families across a wide spectrum of breast cancer risk. The six BCFR sites have

recruited breast cancer families through population-based cancer registries, clinical settings, and community outreach from four areas of the United States: (a) the Greater San Francisco Bay area, California; (b) New York City, New York; (c) Philadelphia, Pennsylvania; (d) Salt Lake City, Utah; (e) the Province of Ontario, Canada; and (f) the metropolitan areas of Melbourne and Sydney, Australia (BCFR, 2013). The BCFR reported recruiting a total of 55,595 individuals for population-based families from 1996-2013, while for the clinic-based families, a total of 14,010 individuals were recruited (BCFR, 2013).

The study population I extracted from the dataset included female patients diagnosed with breast cancer from 1997-2014. The dataset included information on BRCA1 or BRCA2 mutations, ethnicity, gender, and age status, and any diagnosis of pancreatic, colorectal, endometria, and cervical cancer after an initial diagnosis of breast cancer with and without the BRCA1 or BRCA2 mutations. Therefore, this dataset contained the information needed to answer the research questions.

Sampling Procedures

The minimum number within an event was ascertained using a nested case-control approach to assure enough cases as demonstrated below. This nested case-control approach was based on a sampling technique known as incidence density sampling (Checkoway, Pearce, & Crawford-Brown, 1989) or risk sampling (Breslow & Day, 1987). Cases were compared with a subset (a sample) of the "risk set," that is, the cohort members who are at risk who could become a case at the time when each case occurs. By

using this strategy, cases occurring later during the follow-up are eligible to be controls for earlier cases (Szklo & Nieto, 2014). For this study, all cases were drawn from the same cohort, and then the correct number of subjects with second primary cancers was selected and then matched with those without second primary cancers. In RQ1, cases must have had one of the BRCA mutations. For RQ2 with women and RQ3 with women and men, I confirmed that the participating subjects have a BRCA1 or BRCA2 mutation.

The sample consisted of female study participants diagnosed with breast cancer based on certain inclusion criteria. For all research questions, subjects must have been diagnosed with a breast cancer-related second primary cancer, pancreatic, colorectal, endometrium, or cervical during the period from 1997 to 2014. In Table 2, I presented additional criteria stratified by the research questions.

Table 2

Study Sample Inclusion Criteria Stratified by Research Question

Research Question	Inclusion Criteria
RQ 1	Females, with and without *BRCA* mutations
RQ 2	Females, with *BRCA* mutations, with data on age at diagnosis of breast cancer and ethnicity
RQ 3	Males and Females, *BRCA* mutations

Sample Size and Power

The sample sizes for the secondary analyses of BRCA1- and BRCA2-related breast cancer and second primary cancers (pancreatic, colorectal, endometrial, and cervical cancer) were restricted by the size of the BCFR data set; BCFR included only

those with current consent during the follow-up period. For both the population-based families and clinic-based families, the total affected population (exposed males (57) and females (4,136) was 4,193. For the unaffected population, there was a total population of 36,410 (males (13, 343) and females (23, 067) for both the population-based families and clinic-based families (BCFR, 2013).

The OpenEpi Version 3 and XLSTAT software were used to calculate the study statistical power a priori as shown in Table 1. Statistical power of a test may be referred to as the ability of the test to generate an effect or the likelihood that the test will not accept the null hypothesis (no effect; Park, 2008). Houser (2012) noted that in quantitative studies, the standard for determining sample size adequacy is power. Adequate power signifies that there are sufficient study participants to observe a difference in the outcome variable if one exists. Therefore, the calculation of power is a mathematical process and may be calculated prospectively (to determine how many study participants are needed) or retrospectively (to ascertain how much power a sample possessed; Houser, 2012). In Table 3, I present the null and alternate hypotheses associated with each research question.

Table 3

Null and Alternative Hypotheses per Research Question

Research Question	Null Hypothesis	Alternative Hypothesis
RQ 1	There is no relationship between *BRCA* mutation status and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among women with breast cancer.	There is a relationship between *BRCA* mutation status and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among women with breast cancer.
RQ 2	There is no relationship between ethnicity and age status and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among women with *BRCA* related breast cancer.	There is a relationship between ethnicity and age status and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among women with *BRCA* related breast cancer.
RQ 3	There is no relationship between gender and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among men and women diagnosed with *BRCA* related breast cancer.	There is a relationship between gender and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, or cervical, among men and women diagnosed with *BRCA* related breast cancer.

I used CPH for the statistical analyses of time to event given the nested case-control study design. While the effect size is unknown, I estimated it based on previous studies. Also unknown was the time to diagnosis or event. Upon receipt of permission to

access the BCFR data set, I used SPSS version 21 and conducted a posthoc evaluation of the power of the study to identify significant associations should they exist.

I performed an a priori power analysis using the estimated sample size and the proposed analysis using CPH. The minimum number within an event was ascertained using a nested case-control approach to assure enough cases as demonstrated below. This nested case-control approach was based on a sampling technique known as incidence density sampling (Checkoway et al., 1989) or risk sampling (Breslow & Day, 1987). Cases are compared with a subset (a sample) of the risk set; therefore, the cohort members who remain at risk at the time when each case occurs can serve as a control (Szklo & Nieto, 2014). For this study, all cases were drawn from the same cohort; subjects with second cancers and subjects not yet been diagnosed with a second cancer were included. For the RQ1 with only females and in the RQ3 with women with BRCA, I confirmed that the participating subjects have a BRCA1 or BRCA2 mutation. Therefore, I estimated a total sample size of 335 after adjusting for the minimum number of subjects with an event. The OpenEpi Version 3 software was used for sample size analysis, and it was confirmed using the XLSTAT software.

The odds ratio from the number of subjects with an event using the nested case-control approach was 0.026. I used this information to establish the power (1- β) expected with an α (Type 1 error) of 0.05, and an expected minimum sample size of 335. The OpenEpi (2010) “power for cohort studies” calculator provided the adjusted power

presented in Table 4. The XLSTAT calculations of power for the CPH model are presented in Table 5 and Figure 1.

Table 4

Minimum Sample Sizes to Achieve 80% Power

Parameters			Inputs and Results
Two-sided significance level (1- α)			95
Ratio of sample size, Unexposed/Exposed			1:1
Percent of Unexposed with Outcome			5
Percent of Exposed with Outcome:			0.14
Odds Ratio			.026
Risk/Prevalence Ratio			.03
Risk/Prevalence difference			-4.9
	Kelsey	Fleiss	Fleiss with CC*
Sample Size, exposed**	167	165	205
Sample Size, non-exposed**	167	165	205
Total sample size**	334	330	410

Adapted from "Observational Epidemiology (2nd ed) by Kelsey, J. L; Whittemore, A. S; Evans, A. S; & Thompson, W. D. 1996. Oxford University Press. Table 15:12.
Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 &3.19
*CC = continuity correction.
**Sample sizes are rounded to the nearest integer.

Table 5

Power for CPH using XLSTAT

Parameters	Inputs and Results
Event rate (P):	0.026
B(Log(Hazard ratio)):	1
Std dev of X1:	1
R^2 of X1 with other X's:	0.1
Power	0.8
Alpha	0.05

Sample size	335

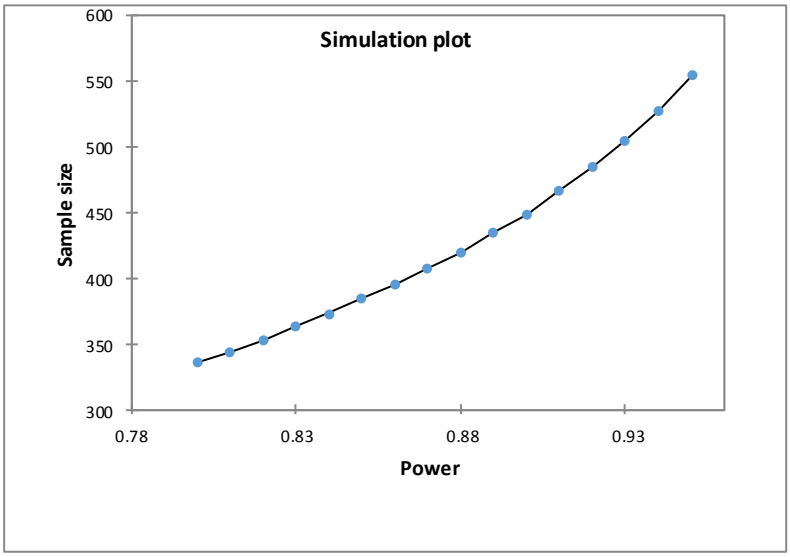

Figure 1. Sample size/power simulation plot I stopped reviewing here due to time constraints.

Instrumentation and Materials

This study used archival data from the NCI- BCFR. BCFR was established in 1995 as pan international research infrastructure for interdisciplinary and translational studies of the genetic epidemiology of breast cancer (John et al., 2004). It is the fundamental objective of BCRF to: "address unanswered research questions regarding the etiology of breast cancer and to expedite the translation of research results to affected and at-risk populations" (John et al., 2004, p.75). The BCFR contains epidemiologic risk factors, clinical, and follow-up data; population-based and clinic-based ascertainment; a combined informatics center; systematic collection of validated family history; and ongoing molecular characterization of the participating families (BCFR, 2013).

Reliability of Data

Quantitative researchers are concerned with reliability and validity to allow them to generalize their findings to other populations. (Houser, 2012). BCFR assures the reliability of data collected in six sites by providing detailed description of research methods, researcher journal, peer examination of procedures and results, and measures of instrument reliability (accuracy and consistency of test instrument and results) (BCFR, 2013). BCFR also uses triangulation, by cross-checking information and conclusions, multiple data sources, and the multiple research methods used by researchers to study the phenomenon in order to ensure the reliability of data collected from study participants (BCFR, 2012).

Validity of Data

Validity helps researchers to ensure that the study measures that which it was intended to measure, or the truthfulness of the result generated (Golafshani, 2003). BCFR has in place several methods of ensuring the validity of data collected from study participants in all six locations across United States, Canada, and Australia. In order to ascertain internal validity, the BCFR employs prolonged engagement (investment of sufficient time in the data collection process to allow the researcher an in-depth understanding of the population under study) (BCFR, 2012), member checking (a method of ensuring validity by having participants review and comment on the accuracy of transcripts, interpretations or conclusions) and triangulation (BCFR, 2013). External validity is sustained by application of inclusion/exclusion criteria and the description of

the setting (BCFR, 2013). All study subjects with complete data will be included, while those with incomplete data will be excluded. Criterion-related predictive validity and content validity have also been used as a test to ascertain the validity in BCFR population and clinical studies (BCFR, 2012). The BCFR procedures used in collecting data is presented in Table 6.

Table 6

BCFR Procedures used to collect Data

Populations	Procedure
Individuals and Families with Breast Cancer Risk	Recruited from a wide spectrum of breast cancer risk
Early-onset Breast Cancer	Families with a history of early-onset breast cancer
Racial and Ethnic Minority Families	Inclusion of all racial and ethnic groups not replicated elsewhere

All included participants were screened based on extensive molecular characterizations active follow-up of both probands and family members. Thus, the BCFR comprises a unique cohort of probands and family members at familial/genetic risk of breast cancer that will continue to facilitate a wide range of research studies, such as gene discovery, examination of cancer-related outcomes and risk factors in high-risk subjects, investigation of novel behavioral interventions, and cancer prevention trials among at-risk family members. (BCFR, 2013).

Data Collection

I conducted this study using data obtained from the National Cancer Institute-Breast Cancer Family Registry (NCI-BCFR) for the years 1997-2014. Data abstraction began after formal approvals from the NCI-BCFR and Walden Institutional Review Boards. The BCFR is a cohort study of families who are at elevated risk of breast and ovarian cancer based on family history or genetic mutations and it contains epidemiologic data on risk factors, clinical and nonclinical variables over time, and family history of participants. It consists of a unique cohort of probands and family members at increased risk of breast cancer. The BCFR population included six participating sites located in the United States, Canada and Australia (John et al.; 2004). United States residing population-based participants were recruited from the Greater San Francisco Bay area, California, United States, by the Northern California Cancer Center. Additionally, population-based families were recruited from the province of Ontario, Canada, by Cancer Care Ontario, and from Melbourne and Sydney, Australia, by the University of Melbourne and the New South Wales Cancer Council. The data used in this study consists of 7,302 breast cancer cases extracted from the six BCFR sites.

Three additional cancer sites were identified and added as mentioned above in order to increase the study power. These included kidney, thyroid, and bladder. Several researchers have investigated the relationship between breast cancer diagnosis and diagnosis of kidney cancer (Dite et al., 2003), thyroid cancer (Dite et al, 2003), and bladder cancer (Neveling et al., 2007; Dite et al., 2010; Dite et al., 2003; Johannesdottir

et al., 1996). BRCA mutations in women diagnosed with breast cancer have also been associated with diagnosis of kidney, thyroid, and bladder cancer (Johanannesdottir et al., 1996).

The study participants were recruited from the six BCFR sites located in the United States, Canada, and Australia (John et al., 2004). United States residing population-based participants were recruited from the Greater San Francisco Bay area, California, United States, by the Northern California Cancer Center. Additionally, population-based families were recruited from the province of Ontario, Canada, by Cancer Care Ontario, and from Melbourne and Sydney, Australia, by the University of Melbourne and the New South Wales Cancer Council.

Clinic-based families were recruited by Columbia University in New York City, the Fox Chase Cancer Center in Philadelphia, and Huntsman Cancer Institute at the University of Utah in Salt Lake City. Clinic based participants in Australia were recruited by the University of Melbourne and New South Wales Cancer Council in Melbourne and Sydney. In Ontario, Canada, recruitment of clinic-based families was limited to those of Ashkenazi Jewish ancestry.

The BCFR data dictionary provided the listing of the various variables in the data set and the explanation of the codes used for case definitions. The study variables available in the BCFR data set were confirmed with their corresponding case definitions in the data dictionary. The BCFR data dictionary consists of over 18 case definitions. These include, AUSTRALIAN DIETARY QUESTIONS, BREAST CANCER

CONFIRMATION, BREAST EPIDEMIOLOGY, BREAST EPIDEMIOLOGY PROCEDURE, BREAST EPIDEMIOLOGY STATUS, BREAST INVASIVE, BREAST MUTATION, BREAST NON-MUTATION, BREAST RX, BREAST SURGERY, CANCER (second cancers), FAMILY PRIMARY, FAMILY MEMBERSHIP, HAWAIIAN DIETARY QUESTION, INDIVIDUAL, NUTRIENT, OVARIAN CONFIRMATION, OVARIAN PATHOLOGY, and PREGNANCY. The data set selection tab was used to select the cases of interest for this study, which included females diagnosed with breast cancer, BRCA1, or/and BRCA2 mutations, and second primary cancers between 1997 and 2014, from the six BCFR sites. This initial selection resulted in 7,302 cases from the data set, which were later merged. Output data files and logs were saved on the home computer.

After the initial selection of cases and merging of data, subjects and records that did not have breast cancer dates were excluded from the list. Second primary cancer cases were identified using the International Classification of Diseases (ICD) for Oncology 2nd edition and filtered for second primary case studies. Subjects who had a second primary cancer after initial diagnosis with breast cancer were considered; whereas, subjects who had second primary cancer diagnosis before diagnosis with breast cancer were excluded. The above inclusion and exclusion criteria resulted in 702 eligible cases for this study. The close date was defined by the event date for subjects who had a second primary cancer. But for the censored events, the close date was arbitrarily taken to be one week after the latest event date in the data set for second primary cancer event

date. The DateDIF function in Microsoft Excel was used to compute the follow up date and event =1 if the subject had second primary cancer after diagnosis with breast cancer and event = 0 otherwise.

Age at diagnosis of breast cancer (AGEDX) was converted from continuous to ordinal variable (Age groups): Less than 46 years = 1, 47-56 = 2, and 57 and older = 3 The rationale was to ascertain the relationship of developing second primary cancers, colorectal, endometrial, cervical, renal, thyroid, or bladder, among women with breast cancer, at different range of age at diagnosis. Breast cancer variable (not mutated) was selected from the data set under Breast RX. It has 4 variants, 0, 1, 2, and 3. Variant 0 stands for the breast cancer not confirmed, but relies on family history provided by relative, variant 1 stands for breast cancer confirmation from death certificate noting cancer of specific site, variant 2 stands for breast cancer confirmation from medical records indicating treatment for cancer of specific site, variant 3 stands for breast cancer confirmation from pathology report indicating tumor site and histology, and variant 4 stands for breast cancer confirmation from histology. Only variants 1 and 2 associated with subjects in the selected case definition for breast cancer diagnosis (Breast_ RX) were used in this study for analyses. BRCA1_PERSON_STATUS and BRCA2_PERSON_STATUS for mutations were coded with 1 for positive diagnosis and 0 for negative diagnosis and used for BRCA1 and BRCA2 variables related analyses. A categorical variable, BRCA both 1 and 2 was created and coded to examine subjects with both BRCA1 and BRCA2 and subjects without both mutations (0). SITE (second

cancers) was selected from the data set under the CANCER case definition. The selected study second cancers ICD codes included C18-C20, for colorectal cancer, C53, for cervical cancer, C54-C55 for endometrial cancer, C64, for renal (kidney) cancer, C73, for cancer of the thyroid gland, and C67, for bladder cancer.

For the race/ethnicity variable, the BCFR data set has 4 variants: RACE_BR1 (obtained from epidemiology question and takes precedence if available), RACE_BR2 (second precedent from other self-reported information), RACE-BR3 (third precedence from questionnaire), and RACE_BR4 (fourth precedence from other sources). RACE_BR1 from the INDIVIDUAL case definition of the data set was selected based on the above criteria. The various ethnicities and races were presented using these codes: 01 for White, 02 for Black, 03 for American Indian and Hawaiian, and 4 for Asian. Other codes such as 10, 99, 70, and 88 were removed due to incomplete or missing data. Three covariates were also included for the analyses: SMOKING (smoking status), BRCA1_FAMILY HISTORY, and BRCA2_FAMILY HISTORY. The dichotomous smoking status variable was coded with 1 for subjects who indicated smoking at least 1 cigarette per day for 3 months or longer and 0 was used for subjects who indicated no smoking history. The dichotomous BRCA1 and BRCA2 family history status were coded with 1 for subjects with positive family history of either *BRCA*1 or *BRCA*2 respectively. Subjects without family history of BRCA1 or BRCA2 were assigned 0.

Data Analysis Plan

Only secondary data was used for this study. Data from cancer patients are confidential, and permission is needed before accessing BCFR data. Access is normally limited by the registry's procedure for research approval and assurance that HIPPA standards are met (BCFR, 2013). A collaboration agreement was submitted and approved before information was released to me (BCFR, 2013). I received data that was free of identifying patient information. The secondary data I proposed to use for this study was extracted electronically and analyzed using SPSS (PASW version 21). SPSS was chosen because of its ability to handle large data sets and its capacity to provide adequate analysis of relevant statistical tests. I cleaned the data after collection of the dataset and prior to my proposed analyses. This data cleaning was necessary to address potential issues such as unreasonable, miscoded, and missing data (Frankfort-Nachmias & Nachmias, 2008). Summary statistics involving frequency and distributions are usually reviewed by BCFR principal investigators at each BCFR site. Set upper and lower and upper parameters was used to query age as the only interval data.

I would have queried and brought unreasonable, missing, or miscoded data to the attention of the BCFR site manager and informatics staff for appropriate validation. Any issue of missing or miscoded data that could not have been settled would have been addressed, depending on the research question and relationship with my study. I included only study subjects with complete data to provide accurate information (yes or no) for those with the dichotomous BRCA variable. All breast cancers was dichotomized to

BRCA1 or BRCA2 mutation breast cancers or non-BRCA1 or BRCA2 mutation breast cancers.

Study Variables

The independent variables that I proposed to use in this study are presented in Table 7.

Table 7

Study Variables

Variable Name	Research Question(s)	Role	Potential Responses	Level of Measurement
Time to Diagnosis of Pancreatic, colorectal, endometrial, and cervical cancer	1, 2, 3	Dependent	Time expressed in Months	Continuous
BRCA Status	1	Independent	*BRCA1* *BRCA2* *BRCA* both 1 and 2	Dichotomous
Ethnicity	2a	Independent	Asian Ashkenazi Jews Black Native-American White	Categorical
Age	2b	Independent	Age in Years	Continuous
Gender	3	Independent	Male Female	Dichotomous
Family History	1,2,3	Covariate	Yes/No family	Dichotomous

Smoking	1,2,3	Covariate	history of *BRCA* Yes/No history of smoking	Dichotomous

Data Analysis

Statistical analyses was carried out using SPSS® 21 statistical software (IBM, 2012). The description was divided by the primary research questions. I also used:

Descriptive statistics. I calculated the descriptive statistics for each of the study variables in table 7. Frequencies were used to describe the dichotomous and categorical variables, while mean and standard deviation were used for the continuous variables age and time to event.

Survival Analysis and Cox Proportional-Hazards (CPH). I used survival analysis techniques, including CPH, to model relationships between dependent and independent variables in the three cohorts. Survival analysis is used to ascertain the probability of the event, also known as incidence proportion (Szklo & Nieto, 2014). Survival analysis mainly explores the relationship of the survival distribution to covariates. The specification of a linear-like model for the log hazard or hazard function is often involved in this analysis (Fox, 2002). According to Fox (2002), the hazard function [*this relation demonstrates h(t)]* formula:

$$h(t) = \lim_{\Delta t \to 0} \frac{\Pr\{t \leq T < t + \Delta t \mid T \geq t\}}{\Delta t}$$

Where t represents the time when observation starts, T shows an outcome event occurrence time and $t + \Delta t$ represents the observation end time. The implication of the

above equation is based on the premise of assumption that the outcome *T* took place after observation time started ($| T \geq t$). Survival analysis targets predictions of the instantaneous risk that a particular outcome will take place at time *t*. By the reason of the continuous nature of time, the probability (Pr) that an outcome will take place exactly at time *t* is necessarily 0. Thus, survival analysis takes into cognizance the likelihood that an event will take place between t and $t + \Delta t$ in a short time interval. Therefore, the denominator presented as a change in t (Δt) assumes the role of divisor that brings together the amount of time within that interval to increase precision. A fundamental disadvantage to the above hazard function is that the hazards in both the exposed and the reference groups may be approximately constant (Szklo & Nieto, 2014). This is the appropriate test because the research questions include time to diagnosis. Logistic regression can only examine the relationship of the independent variables to whether there was a diagnosis of second cancer, and not to how long after the diagnosis of breast cancer that it occurred. CPH provides hazard ratios, which are defined as an estimate of the ratio of the hazard rate in patients with BRCA and non-BRCA breast cancer. The hazard rate represents the likelihood that if the event in question has not already occurred, it is expected to occur in the next time interval, divided by the length of the interval (Spruance, Reid, & Samore, 2004).

Bivariate Tests. The log-rank test was used to identify significant differences in the median time to event between BRCA status, ethnicity, family, and smoking histories and time to diagnosis of second primary cancers, colorectal, endometrial, cervical,

kidney, thyroid, and bladder among women with breast cancer. Spearman correlation was used to test the relationship between time to event and age.

Test of Proportionality. Survival analysis was used to test the assumption of proportional risks required to use CPH. I graphed survival times for those with and without risks to test proportionality. Risks are not proportionate if the survival times cross each other within the period graphed. If this happens, I may need to perform separate tests, before and after the cross, to generate valid hazard ratios (Szklo & Nieto, 2014). An example of the test of proportionality is presented in Figure 2.

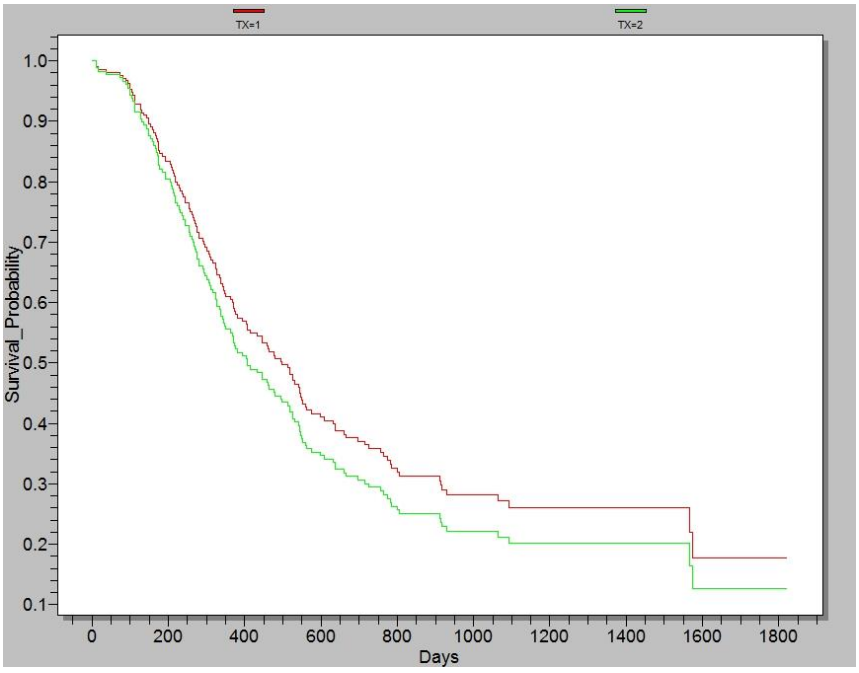

Figure 2. Kaplan-Maier Curves

Curves used for analysis of the assumption of proportionality in two arms of a clinical trials protocol. The green curve shows the hazards or failure in the placebo arm and the red curve shows the hazards or failure in the experimental of the above clinical

process. Adapted from “Association between Diabetes Incidence and Metabolic Syndrome in Western Alaska Native People”, by K. R. Koller (2013), *ProQuest*, p.132. Adapted with permission.

Time to event. The time to event for all research questions was the time between the diagnosis of breast cancer and the diagnosis of either of the following second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder**.** The time was expressed using months. Because not only those participants who developed the second primary cancers were included in the dataset, there was need for censoring. Entry was based on the diagnosis of breast cancer and exit on the diagnosis of second primary cancers. For each of the following three research questions, I examined the associations between time to event and the independent variables listed in table 7. These associations was addressed using the cohorts presented in Table 1.

Research Question 1

Is there a relationship between BRCA mutation status and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer? The objective was to ascertain the relationship and time to event of developing second primary cancers, specified as, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with BRCA related breast cancer and those with non BRCA related breast cancer. Second cancers are cancers that develop after initial diagnosis with BRCA1 or BRCA2 related breast cancer. A single hypothesis was tested to ascertain this relationship.

H_0: There is no relationship between BRCA mutation status and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer.

H_a: There is a relationship between BRCA mutation status and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer.

Research Question 2

Is there a relationship between ethnicity and age status and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with BRCA related breast cancer? The objective was to ascertain the relationship of developing second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with BRCA related breast cancer, their ethnicity and age at diagnosis. This research question required two hypothesis statements.

Is there a relationship between ethnicity and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with BRCA related breast cancer?

Is there a relationship between age status and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women BRCA related breast cancer?

One hypothesis was tested to ascertain this relationship:

H_0: There is no relationship between ethnicity and age status and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with BRCA related breast cancer.

Ha: There is a relationship between ethnicity and age status and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with BRCA related breast cancer.

Research Question 3

Is there a relationship between gender and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among men and women diagnosed with BRCA related breast cancer? The objective was to ascertain the relationship of developing second primary cancer, pancreatic, colorectal, endometrial, or cervical, among men and women with BRCA related breast cancer and gender. Because of no availability of male gender data in the data set, the relationship between gender and time to diagnosis of second primary cancers was not analyzed. A single hypothesis was intended to be tested to ascertain this relationship.

H_0: There is no relationship between gender and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among men and women diagnosed with BRCA related breast cancer.

H_a: There is a relationship between gender and time to diagnosis of second primary cancers, , colorectal, endometrial, cervical, kidney, thyroid, or bladder, among men and women diagnosed with BRCA related breast cancer.

Threats to Internal and External Validity

It is important to balance control of threats to internal validity with the need to maximize external validity. Generalization remains a major issue for research that is to be used as evidence (Houser, 2012). When a research study becomes too highly controlled, its artificial nature limits applicability to real-world populations. The research must balance each element that strengthens internal validity with a concern to maintain as broad of external validity as possible (Houser, 2012).

BCFR database is recognized as a standard for quality research. Quality assurance remains the mainstay of all the six participating sites (BCFR, 2013). BCFR minimizes threats to internal validity by encouraging studies that create logical and evidence-based research, collecting data to support such research, using appropriate design, and controlling bias (BCFR, 2013). Threats to external validity are minimized by maintaining the generalizability of the findings of their various studies to other populations or settings (BCFR, 2013).

Ethical Considerations

According to BCFR (2013), each of the six participating research sites has an Institutional Review Board (IRB) that reviews the study protocol and questionnaires, identifying issues and concerns, and works with the investigators as needed to improve the study. The IRB at each site is diverse and includes ethicists, lawyers, physicians, scientists, and community members. The researchers and staff who are conducting the study are provided with regular monitoring and education to ensure that these

requirements are met (BCFR, 2013). BCFR has provided several protections for the privacy of study participants and their respective data (BCFR, 2013). When study participants data are collected, they are usually assigned a unique identification (ID) number. After data collection, the bio-specimen samples, questionnaires, and interview data are stored separately from any personal identifiers, such as patient's name, address, and phone number. Personal contact information of the study subjects are kept in separate files available only to the research staff at the specific site where they participate. When data are used for analytical purpose, the randomly assigned numeric ID is the only identifier available to investigators (BCFR, 2013).

A Certificate of Confidentiality is normally provided to each of the six BCFR sites to protect the confidentiality of data against compulsory legal demands (e.g., court orders and subpoenas) that may seek the name or other identifying characteristics of a research subject. With a Certificate of Confidentiality, researchers cannot be mandated by anyone to provide information that could identify the study participants (BCFR, 2013). BCRF also requires researchers interested in using its data to submit an application for a short-term data agreement/collaboration. This is to ensure quality research procedures are followed as well as to maintain confidentiality of study data. Collaborating researchers are encouraged to work closely with the BCFR liaison, throughout the design phase of their studies (BCFR, 2013)**.** Additionally, a Walden University IRB application was submitted for this study and an approval was also received. The IRB approval number for this study was 02-23-15-0085556**.**

Summary

In this chapter, I presented the methodology for the proposed study. I conducted secondary data analyses using a nested case-control study design. The study population included female patients diagnosed with breast cancer from 1997-2014. The population also included females diagnosed with BRCA1 or BRCA2 mutations, with data on ethnicity, and age status. Three other covariates were included and analyzed: Smoking status, and BRCA1/BRCA2 family history. The BCFR data set also included only female patients diagnosed with second cancers (including pancreatic, colorectal, endometrial, and cervical cancer) after initial diagnosis with BRCA1 or BRCA2 mutation. Three other cancer sites were included in order to increase the sample size: Kidney, thyroid, and bladder. The study was intended to involve the application of survival analysis to look for associations at the bivariate level and to test the associations between the time to diagnosis with second primary cancers including colorectal, endometrial, cervical, kidney, thyroid, and bladder cancer and risk factors specified in this chapter using Cox proportional hazards regression. This was the appropriate test because the research questions were about time to diagnosis of second primary cancers such as colorectal, endometrial, cervical, kidney, thyroid, and bladder cancer among subjects diagnosed with breast cancer. The results of this study are presented in Chapter 4.

Chapter 4: Results

Introduction

The purpose of this quantitative study was to investigate the association of gender, ethnicity, and age of diagnosis of breast cancer with risk of diagnosis of second primary cancers, including pancreatic cancer, colorectal cancer, endometrial cancer, and cervical cancer, among subjects diagnosed with breast cancer. A composite endpoints approach was used in defining events and testing the stated associations. It was necessary to make some changes from the original data plan. An additional three cancer sites (kidney cancer, thyroid cancer, and bladder cancer) were added in order to increase the sample size and power of the study. Pancreatic cancer was not among the variables analyzed because no subject with pancreatic cancer in the BCFR study population met the inclusion criteria. Gender as an independent variable was not included in the analysis because the data set did not include any male subjects.

This chapter starts with the presentation of the results of the baseline descriptive and demographic characteristics of each variable. The chapter continues with the presentations and descriptions of the results of the Kaplan Meier (KM) survival analyses and CPH to answer the stated research questions. The chapter concludes with recapitulation of the summary of the results.

The first research question (RQ1) after including the additional three cancer sites was the following:

1. Is there a relationship between BRCA mutation status and the risk of diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer?

H_{01}: There is no relationship between BRCA mutation status and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, renal, thyroid, or bladder, among women with breast cancer.

H_{a1}: There is a relationship between BRCA mutation status and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer.

2. Is there a relationship between ethnicity and age status and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid or bladder, among women with breast cancer?

H_{02}: There is no relationship between ethnicity and age status and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, renal, thyroid, or bladder, among women with breast cancer.

Ha_2: There is a relationship between ethnicity and age status and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer.

In each case, differences in median time distributions were examined using the KM survival curves and tested using the log-rank test, except during the analysis of age

group and time to diagnosis of second primary cancers, where the Spearman correlation was used to test the relationship between time to event and age.

Baseline Characteristics of the Sample

The epidemiological data included the following independent variables: BRCA status, ethnicity, and age. They also included the BRCA both 1 and 2 (for subjects with two BRCA mutations) and covariates smoking, BRCA1 family history, BRCA2 family history, and time to diagnosis of second primary cancers. A sample data line is shown in Table 6 of Chapter 3.

The descriptive statistics for the study sample are presented in Table 8.

Table 8

Descriptive Statistics of the Study Sample (N = 702) from the BCFR 1997-2014 Dataset

Variable	Responses	Frequency	Percent
Age	<46 years	136	16.2
	47-56 years	196	27.9
	57 and older	370	52.7
Breast cancer variants	1 or 2	702	100
BRCA1 person status	Yes	528	75.2
BRCA2 person status	Yes	539	76.8
BRCA status both 1 and 2	Yes	500	71.2
Race/Ethnicity	White	551	78.5
	Black	71	10.1
	American Indian	4	0.06
	Asian	76	10.8
Event	Yes second cancer	81	11.5
Site	Colon and rectum	22	3.98
	Cervix	5	0.9
	Endometrium	32	5.76
	Kidney	5	0.9
	Bladder	8	1.44
	Thyroid	9	1.62
Smoking	Yes	302	43.0
BRCA1 Family history	Yes	483	68.8
BRCA2 Family history	Yes	501	71.4
Continuous variable	Number	Mean	Standard deviation
Time to event	702	12.73	3.642

Results

The results are divided into three sections, arranged according to research question and additional findings from the covariates. Table 7 in Chapter 3 presented how each of the study variables was used to answer the two research questions.

Research Question 1

The first research question's (RQ1) results of this analysis are summarized in Table 9, Table 10, and Table 11.

Table 9

Mean and Median Survival Time by BRCA1 (n = 702)

Breast Ca Gene Mutation (n)	Mean	SD*	Median	IQR
*BRCA*1 = 0 (174)	12.546	1.1	14.000	0.4
*BRCA*1 = 1 (528)	12.792	0.6	14.000	0.2
Overall	12.731	0.5	14.000	0.2

Note. Estimation is limited to the largest survival time if it is censored

Table 10

Mean and Median Survival Time by BRCA2 (n = 702)

Breast Ca Gene Mutation (n)	Mean	SD*	Median	IQR
*BRCA*2 = 0 (163)	12.724	1.2	14.000	0.8
*BRCA*2 = 1 (539)	12.733	0.6	14.000	0.2
Overall	12.731	0.5	14.000	0.2

Note. Estimation is limited to the largest survival time if it is censored

Table 11

Mean and Median Survival Time by BRCA Both 1 and 2 (n = 702)

Breast Ca Gene Mutation (n)	Mean	SD*	Median	IQR
BRCA both 1 and 2 = 0 (202)	12.663	1.1	14.000	0.4
BRCA both 1 and 2 = 1 (500)	12.758	0.7	14.000	0.2
Overall	12.731	0.5	14.000	0.2

Note. Estimation is limited to the largest survival time if it is censored

As Table 9, Table 10, and Table 11 show, the interquartile range of BRCA1, BRCA2, and BRCA both 1 and 2 are the same [0.2]. The BRCA1, BRCA2, and BRCA both 1 and 2 have the same overall time to event of 14.000 years. The BRCA1, BRCA2, and BRCA both 1 and 2 demonstrate the same median time to event of 14.000 years. The overall interquartile range of the BRCA1 was [0.2], and the overall interquartile range of BRCA2 was [0.2], while the overall interquartile range of BRCA both 1 and 2 was also [0.2]. The log- rank test for BRCA1 = 0.797, with $p = 0.372$, and the log-rank test for BRCA2 = 1.808, with $p = 0.179$, while the log-rank test for BRCA both 1 and 2 = 0.001, with $p = 0.972$. The BRCA1, BRCA2, and BRCA both 1 and 2 results were not statistically significant.

The survival curves by BRCA1, BRCA2, and BRCA both 1 and 2 were generated using the KM survival curve as shown in Figure 3, Figure 4, and Figure 5, respectively.

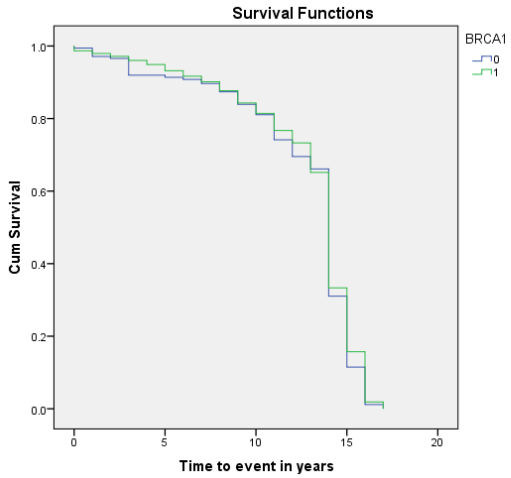

Figure 3. KM's survival curve for BRCA1 (*p*-value = 0.372)

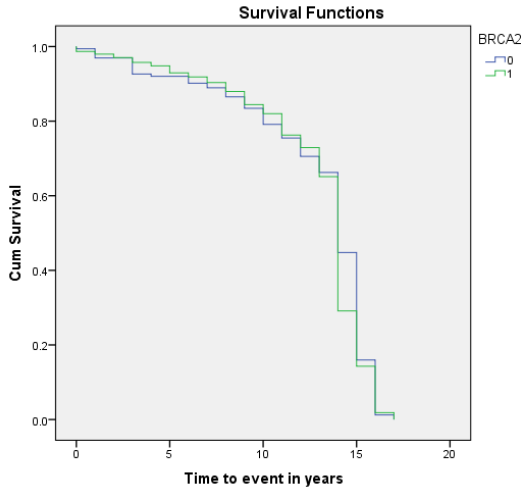

Figure 4. KM's survival curve for BRCA2 (*p*-value = 0.179)

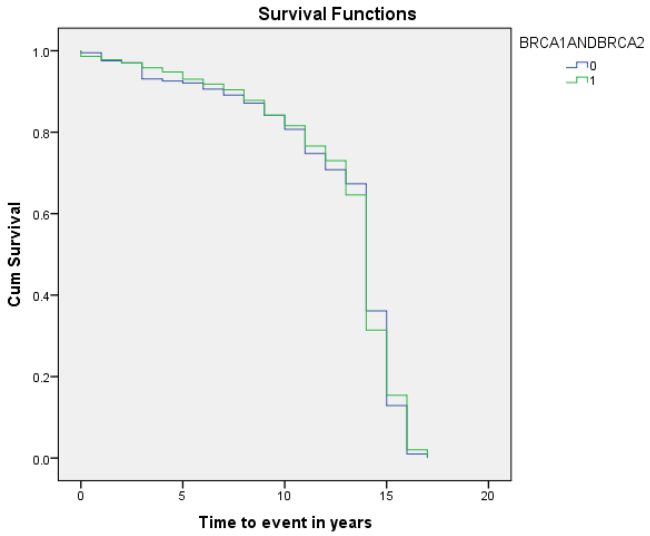

Figure 5. KM's survival curve for BRCA both 1 and 2 (*p*-value = 0.179)

The above three KM's survival curves show that the median time to event for BRCA1, BRCA2, and BRCA status both 1 and 2 are the same at 14 years respectively.

Stratification of breast cancer by BRCA status both 1 and 2. The survival by different levels of the variable was compared by adding yet another layer of adjustment (control) in a model. Stratification by BRCA status both 1 and 2 variable was conducted. This was done with the breast cancer in the factor position, BRCA status both 1 and 2 variable in the strata position, and time to event in years in the time position and events (with second cancers) in the event position of the analysis. Because the probability of survival changes over time, stratification enabled survival patterns to be compared at various stages or observation times (Szklo & Nieto, 2014).

Table 12 presents a mean and median difference in survival after stratification of the breast cancer by BRCA status both 1 and 2.

Table 12

Mean and Median Survival Time by BRCA Both 1 and 2 After Stratification (n = 702)

Breast Ca Gene Mutation	Breast Cancer	Mean	SD*	Median	IQR
BRCA both 1 and 2 = 0	1	12.730	1.04	14.000	0.42
BRCA both 1 and 2 = 1	2	6.000		6.000	
	Overall	12.663	1.05	14.000	0.42
BRCA both 1 and 2 = 0	1	12.757	0.63	14.000	
BRCA both 1 and 2 = 1	2	13.000		13.000	
	Overall	12.758	0.63	14.000	0.23
Overall	Overall	12.731	0.44	14.000	0.23

Note. Estimation is limited to the largest survival time if it is censored

After stratification as shown in Table 12, interquartile range of breast cancer (1) with BRCA both 1 and 2 (0) = 0.42, with time to event = 14 years, while breast cancer (2) with BRCA both 1 and 2 (1) has time to event of 6 years and 13 years respectively. Both breast cancer ((1) and (2)) and BRCA both 1 and 2 ((0) and (1)) have overall time to event estimate = 14.0 years. The log-rank test was used to ascertain the significant differences in the time to event for patients with breast cancer. The log-rank test of equality for the breast cancer = 8.849 and $p = 0.003$. This was statistically significant.

Figure 6 and Figure 7 show the survival function curves for breast cancer after stratification with BRCA both 1 and 2. Figure 6 presents the curve when BRCA both 1 and 2 is 0, while Figure 7 shows when that value is 1.

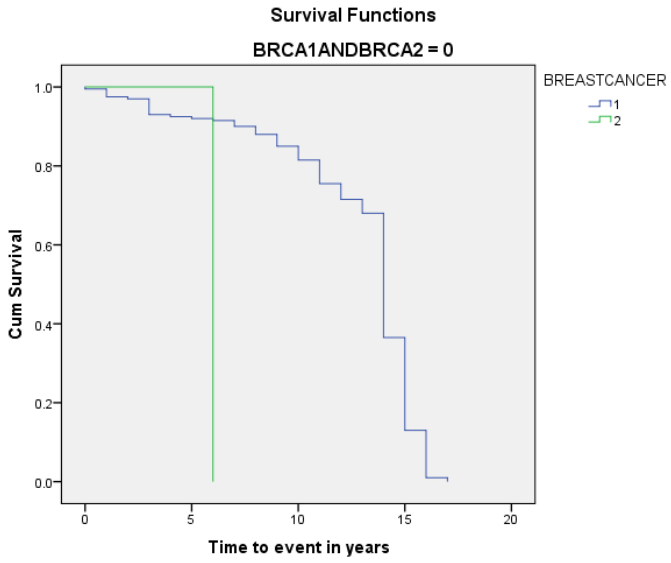

Figure 6. KM's survival curve for breast cancer after stratification with BRCA both 1 and 2 (*p*-value = 0.003)

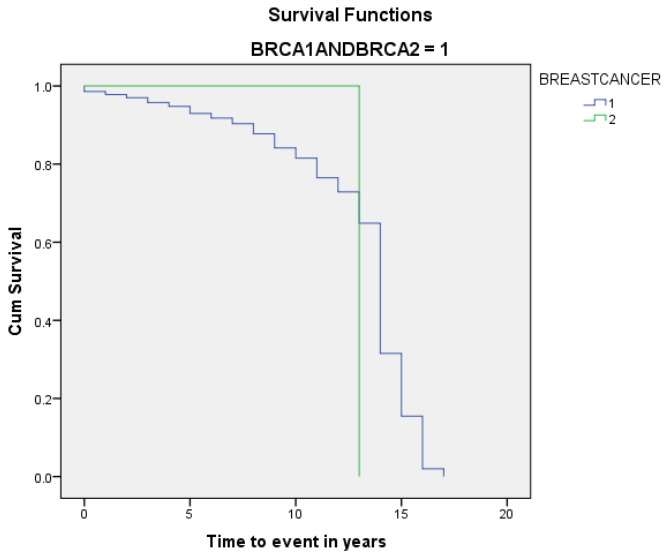

Figure 7. KM's survival curve for breast cancer after stratification with BRCA both 1 and 2 (*p*-value = 0.003)

Hazard ratio and the test of proportionality. I performed a Cox regression analysis to estimate the hazard ratio for the breast cancer gene mutations, BRCA1, BRCA2, and BRCA both 1 and 2. Here, I employed the composite endpoint (event) analysis due to the sparsity of events for the various second primary cancer sites. The hazard ratio generated will be the measure of association in this case. A composite endpoint (outcome) consists of two or more component outcomes (in the above case, colorectal, endometrial, cervical, kidney, thyroid, and bladder cancer). Patients who have experienced any one of the events specified by the components are considered to have experienced the composite outcome. The hazard ratios for BRCA1 and BRCA2 were determined. The Cox proportional hazards regression model is based on the proportional hazards assumption. An assessment of as to whether this assumption was met or not was done using the KM's curves

Table 13 shows the parameters for the Cox proportional hazard model for BRCA1, BRCA2, and BRCA both 1 and 2 gene mutations after adjusting for covariates.

Table 13

Cox Hazard model for Breast Cancer, BRCA1, BRCA2, and BRCA both 1 and 2 (n = 702)

Breast Ca and *BRCA* mutations	Hazard ratio	95% Confidence interval
Breast Ca unadjusted	4.031	(1.50, 10.84)
Adjusted	4.252	(1.56, 11.44)
*BRCA*1	0.781	(0.529, 1.17)
*BRCA*2	1.471	(1.03, 2.11)
BRCA both 1 and 2	0.891	(0.53, 1.50)

Table 13 shows hazard ratio for breast cancer unadjusted was 4.031, 95% Confidence Interval (CI) hazard ratio [1.50 -10.84], was statistically significant. This means that over 16 years of follow-up, the hazard for second primary cancers risk among patients diagnosed with breast cancer was 4.031 times higher than those not diagnosed with breast cancer. The hazard ratio of.BRCA1 mutation was 0.78, 95% CI hazard ratio [0.52 – 1.17], was not a statistically significant result. This means that over 16 years of follow-up, the hazard for second primary cancers risk among patients diagnosed of BRCA1 gene mutations was 7.8 times higher than those not diagnosed with breast. The BRCA2 mutation hazard ratio was 1.471 with 95% CI hazard ratio = [1.03 – 2.11]. This was statistically significant. This means that over 16 years of follow-up, the hazard for second primary cancers risk was 14.7 times higher than those not diagnosed with breast cancer. The BRCA both 1 and 2 mutations hazard ratio was 0.891, with a corresponding 95% CI hazard ratio [0.53 – 1.50] was not statistically significant. This means that over 16 years of follow-up, the hazard for second primary cancers risk was 8.9 times higher in the population under study. Therefore, I failed to reject the null hypothesis of no relationship between BRCA1 and BRCA both 1 and 2 and time to diagnoses of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid or bladder, among women with BRCA related breast cancer. However, I rejected the null hypothesis of no relationship between BRCA2 and time to diagnoses of second primary cancers,

colorectal, endometrial, cervical, kidney, thyroid or bladder, among women with BRCA related breast cancer.

In both the unadjusted and adjusted model, there is an increased risk of second primary cancers among participants with breast cancer (hazard ratio of 4.031, 4.252) as compared to those with BRCA1 and BRCA both 1 and 2. However, after adjustment for BRCA1 and BRCA both 1 and 2, there is no statistically significant difference between participants in terms of (hazard ratio = 0.781, p = 0.5038, hazard ratio = 0.891, p = 0.667). The same is not true in the model adjusting for the BRCA2 risk factor. However, after adjustment, the difference in BRCA2 participants remains statistically significant, with hazard ratio of 1.471, p = 0.036, as compared to other participants. The hazard ratio by each breast cancer mutation genes, BRCA1, BRCA2, and both BRCA1 and BRCA2 were generated using the Cox regression model. The test of proportionality that was checked with Kaplan-Meier curves showed hazards are proportional within the groups. The CPH assumption was met.

Research Question 2

The second research question's (RQ2) was divided into two. The first is:

RQa. Is there a relationship between ethnicity and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, thyroid, or bladder, among women with BRCA related breast cancer?

RQb. Is there a relationship between age group and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, thyroid, or bladder, among women BRCA related breast cancer?

The results of these analyses are summarized in Table 14 and Table 15

Table 14

Mean and Median Survival Time by Race/Ethnicity (n = 702)

Race/Ethnicity (n)	Mean	SD	Median	IQR
White (551)	12.964	0.62	14.000	0.22
Black (71)	11.634	1.49	11.000	1.94
American I/H (4)	15.000	2.76	15.000	3.56
Asian (76)	11.947	1.48	12.000	2.44
Overall (702)	12.731	0.54	14.000	0.22

Note. Estimation is limited to the largest survival time if it is censored

Table 15

Mean and Median Survival by Age Groups (n = 702)

Age groups (n)	Mean	SD	Median	IQR
<46 years (136)	12.765	1.14	14.000	0.40
47 – 56 years (196)	12.668	1.06	14.000	0.36
57 years and older (370)	12.751	0.74	14.000	0.34
Overall (702)	12.731	0.54	14.000	0.22

Note. Estimation is limited to the largest survival time if it is censored

As Table 14 shows, there are observed statistically significant differences for White and American Indian/Hawaiian (American I/H) race/ethnicity except for “Black” and “Asia” race/ethnicity. Of note, are the time to event estimates for race/ethnicity,

White = 14.000, Black = 11.000, American I/H = 15.000, and Asia = 12.000. Race/Ethnicity has overall time to event = 14.000. The log rank test of equality was 29.482 with a corresponding p = 0.000. This was statistically significant.

As Table 15 shows, there are no observed statistically significant differences in the age groups according to the interquartile range of survival by age groups. Of note, are the time to event estimates for age groups, <46 years = 14.000, 47-56 years = 14.000, and 57 years and older = 14.000 years. Age groups have overall time to event = 14.000 years. The Spearman correlation coefficient $r_s = 0.026$. This is not statistically significant (p = 0.487). In the same manner, there was no statistical significant result observed after looking at the Spearman correlation with age at diagnosis without grouping the participants into age groups as well. The Spearman correlation coefficient r_s was 0.018 (p = 0.627).

Table 16 shows the nonparametric Spearman rank order correlation coefficient sample which was used to test the relationship between age groups and time to event.

Table 16

Spearman Correlation Test for Age groups and Time to event (n = 702)

		Age group
Time to event	Correlation Coefficient	0.026
	Sig. (2-tailed)	0.487

Table17 shows the nonparametric Spearman rank order correlation coefficient sample which was used to test the relationship between age and time to event.

Table 17

Spearman Correlation Test for Age at Diagnosis (not grouped) and Time to event (n = 702)

		Age group
Time to event	Correlation Coefficient	0.018
	Sig. (2-tailed)	0.627

In Figure 8 and Figure 9, I present the survival by race/ethnicity and age groups using the KM's survival curve of differences between times to event of second primary cancers.

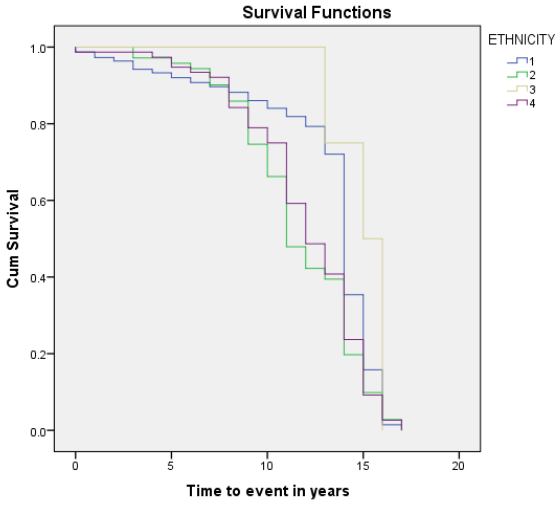

Figure 8. Kaplan Meier's survival curve of Race/Ethnicity, p = 0.000, 1 = White (includes the Ashkenazi Jews), 2 = Black, 3 = American I/H, and 4 =Asian

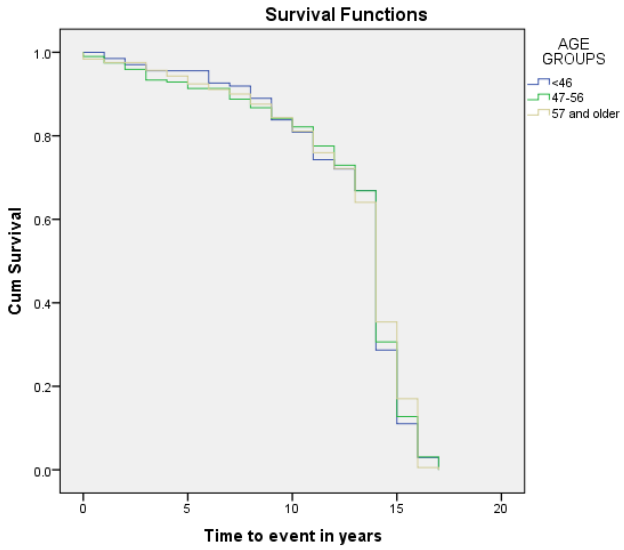

Figure 9. Kaplan Meier's survival curve of Age groups, p = 0.487

As presented in Figure 9, both race/ethnicity and age groups have the same overall median time to event of 14 years.

Hazard ratio and the test of proportionality. I performed a Cox regression analysis to determine the hazard ratio for race/ethnicity and age groups. I employed the composite endpoint (event) analysis due to the sparsity of events for the various second primary cancer sites. The hazard ratio generated will be the measure of association in this case. The assumption of proportional risks required to use CPH was also checked with Kaplan-Meier curves.

Table 18 shows the CPH of the samples with hazard ratios.

Table 18

Cox Hazard model for Race/Ethnicity and Age groups (n =702)

Ethnicity and age groups		Hazard ratio	95% Confidence interval
Ethnicity	White	1.511	(1.88, 1.94)
	Black	0.647	(0.23, 1.67)
	American I/H	1.424	(1.12, 1.81)
	Asian	Ref.	
Age group	<46 years	0.942	(0.76, 1.17)
	47-56 years	0.925	(0.76, 1.13)

In Table 18, Asian race is the referent group. The hazard ratios for White (includes the Ashkenazi Jews) and American I/H at 95% CIs hazard ratio [1.17 – 1.93] and [1.12 – 1.81] are statistically significant, while the hazard ratio for Black was not a statistically significant result [0.742 – 1.730]. This means for over 16 years of follow-up, the hazard ratio for second primary cancers risk among White and American I/H races diagnosed of breast cancer were 15.1 times and 14.2 times respectively higher compared to the reference group (Asian race). Over the same follow-up years, the hazard ratio for second primary cancers risk among Black race was 6.5%. This implies that both White (includes the Ashkenazi Jews) and American I/H (though there are really too few of those to have any meaningful results are significantly different, but that Blacks and Asians are not. Therefore, I rejected the null hypothesis of no relationship between race/ethnicity (White and American I/H) and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid and bladder. I also failed to reject the null

hypothesis of no relationship between Black race and Asian race and diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid and bladder.

For age groups, 57 years and older is the referent group. The hazard ratios for <46 years and 47-56 years at 95% CIs [0.76 – 1.17] and [0.76 – 1.13] are not statistically significant. This means for over 16 years of follow-up, the hazard ratio for second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder risk of diagnosis among age group <46 years and 47-56 years was 6.7 times higher compared to the reference group. This implies though 57 and older have greater number, they may not also be statistically significant. Therefore, I failed to reject the null hypothesis of no relationship between age group and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid and bladder. The test of proportionality that was checked using the KM's curves showed hazards are proportional within the groups. The CPH assumption was met.

When I analyzed race/ethnicity without merging all the Asian races into one as demonstrated in the above analyses, the following results were generated as shown in Table 19

Mean and Median Survival Time by Race/Ethnicity (without merging) (n = 702)

Race/Ethnicity (n)	Mean	SD	Median	IQR
White (includes the Ashkenazi Jews)	12.964	0.62	14.000	0.22

Black	11.634	1.49	11.000	1.94
American Indian	15.000	2.72	15.000	3.56
Chinese	12.421	1.88	12.000	3.44
Japanese	10.400	3.75	10.000	4.04
Filipinos	11.957	3.10	13.000	3.10
Asian	12.500	6.09	13.000	1.76
Overall	12.731	0.54	14.000	0.21

Note. Estimation is limited to the largest survival time if it is censored

As Table 19 shows, the number (n) for Asian is 76, then it is likely I do not have enough data to draw any conclusions on the Asian sub groups. This evidence is provided based on an analysis of the survival times for the various Asian races represented to suggest that combining them as I demonstrated did not significantly alter my results from the previous analysis.

Adjusting for Confounders

In RQ2a, I presented that race/ethnicity was a confounder. In order to further examine this, I evaluated BRCA status using the confounder in the analysis. I reevaluated the relationship between BRCA gene mutations (BRCA1, BRCA2, and BRCA both 1 and 2) and White (includes the Ashkenazi Jews) to American I/H race by conducting

multivariate test (CPH) to see if there could be a difference. The test of proportionality was checked using the KM's curves.

Table 20 shows the CPH of the samples with hazard ratios.

Table 20

Cox Hazard model for Confounder Race/Ethnicity and BRCA status (BRCA1, BRCA2, and BRCA both 1 and 2) (n =702.

BRCA status	Race/Ethnicity	Hazard ratio	95% Confidence interval
*BRCA*1		0.867	0.73, 1.04
	White	1.559	1.21, 2.01
	Black	0.673	0.25, 1.80
	American I/H	1.476	1.16, 1.87
	Asian	Ref.	
BRCA 2		1.025	0.86, 1.23
	White	1.495	1.16, 1.92
	Black	0.642	0.24, 1.72
	American I/H	1.414	1.12, 1.81
	Asian	Ref.	
BRCA 1 and 2		0.925	0.78, 1.10
	White	1.537	1.19. 1.98
	Black	0.664	0.25, 1.78
	American I/H	1.459	1.14, 1.87
	Asian	Ref.	

Table 20 shows hazard ratio for White race when analyzed with BRCA1 was 1.559, 95% CI hazard ratio [1.21 - 2.01], was statistically significant. This means that over 16 years of follow-up, the hazard for second primary cancers risk among White race

diagnosed of BRCA1 gene mutation was 15.6 times higher compared to the reference group (Asian race). The hazard ratio for Black race with BCA1 was 0.673, 95% CI hazard ratio [0.25 – 1.80] was not statistically significant. This means for over 16 years of follow-up, the hazard ratio for second primary cancers risk among Black race diagnosed of BRCA1 gene mutation was 6.7 times higher compared to the reference group (Asian race). The hazard ratio for American I/H races with BCA1 was 1.476, 95% CI hazard ratio [1.16 – 1.87] was statistically significant. This means for over 16 years of follow-up, the hazard ratio for second primary cancers risk among the American I/H races diagnosed of BRCA1 gene mutation was 14.8 times higher compared to the reference group (Asian race).

The hazard ratio for White race (includes the Ashkenazi Jews) when analyzed with BRCA2 was 1.495, 95% CI hazard ratio [1.16 – 1.92], was statistically significant. This means that over 16 years of follow-up, the hazard for second primary cancers risk among White race diagnosed of BRCA2 gene mutation was 15.0 times higher compared to the reference group (Asian race). The hazard ratio for Black race when analyzed with BRCA2 was 0.642, 95% CI hazard ratio [0.24 – 1.72], was not statistically significant. This means that over 16 years of follow-up, the hazard for second primary cancers risk among Black race diagnosed of BRCA2 gene mutation was 6.4 times higher compared to the reference group (Asian race). The hazard ratio for American I/H races when analyzed with BRCA2 was 1.415, 95% CI hazard ratio [1.12 – 1.81], was statistically significant. This means that over 16 years of follow-up, the hazard for second primary cancers risk

among American I/H races diagnosed of BRCA2 gene mutation was 14.2 times higher compared to the reference group (Asian race).

The hazard ratio for White race when analyzed with BRCA both 1 and 2 was 1.537, 95% CI hazard ratio [1.19 – 1.98], was statistically significant. This means that over 16 years of follow-up, the hazard for second primary cancers risk among White race diagnosed of BRCA both 1 and 2 gene mutations was 15.4 times higher compared to the reference group (Asian race). The hazard ratio for Black race when analyzed with BRCA both 1 and 2 was 0.664, 95% CI hazard ratio [0.25 –1.78] was not statistically significant. This means that over 16 years of follow-up, the hazard for second primary cancers risk among Black race diagnosed of BRCA both 1 and 2 gene mutations was 6.6 times higher compared to the reference group (Asian race). The hazard ratio for American I/H races when analyzed with BRCA both 1 and 2 was 1.459, 95% CI hazard ratio [1.14 – 1.87], was statistically significant. This means that over 16 years of follow-up, the hazard for second primary cancers risk among American I/H races diagnosed of BRCA both 1 and 2 gene mutations was 14.6 times higher compared to the reference group (Asian race).

The result summary showed that race/ethnicity as a confounder may have a relationship with diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder in the population under study. The KM's curves showed hazards are proportional within the groups. The CPH assumption was met.

Adjusting for Covariates

The relationship between the study covariates such as smoking status, BRCA1 family status, and BRCA2 family status and time to event of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, and bladder were also analyzed. The survival by each of the covariates was generated using the KM's survival curve of differences between time of diagnosis with breast cancer and time to event of second primary cancers. The log-rank test was used to identify significant differences in the median time to event. The hazard ratios of the covariates were determined and the assumption of proportional risks required to use CPH was also checked.

Smoking Status

Table 21 shows the summary of the smoking status analysis.

Table 21

Mean and Median Survival Time by Smoking status (n = 702)

Race/Ethnicity (n)	Mean	SD	Median	IQR
Smoking = 0 (400)	12.975	0.67	14.000	0.3
Smoking = 1 (302)	12.407	0.88	14.000	0.33
Overall (702)	12.731	0.74	14.000	0.22

Note. Estimation is limited to the largest survival time if it is censored

As Table 21 shows, there are observed no statistically significant differences in the relationship between smoking status and time to diagnosis of second primary cancers. Of note, are the median time to event estimates at 95% CIs and overall time to event estimates of both Smoking (0) and Smoking (1) are 14.000 years respectively. The log-

rank test for smoking status was 1.844, and p = 0.174 and did not show any statistical significance.

Figure 10 shows the KM's survival curve for smoking status and time to diagnosis of second primary cancers.

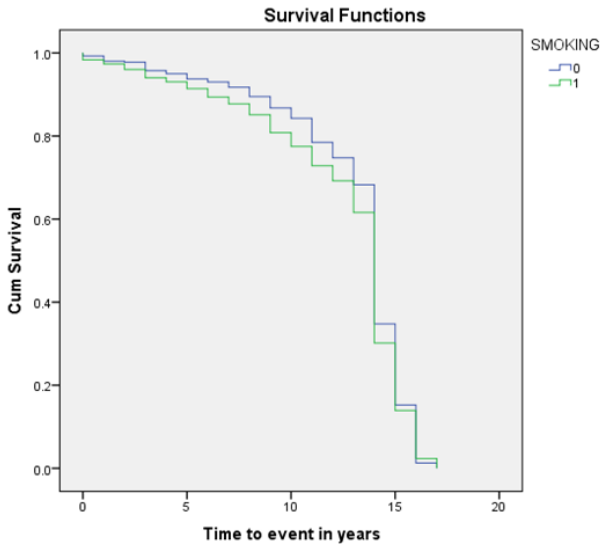

Figure 10. KM's survival curve of Smoking status (p-value = 0.174).

BRCA1/BRCA2 Family Status

BRCA1/BRCA2 family status and time to event. The survival by each BRCA1 family status and BRCA2 family status was generated using the KM's survival curve of differences between times to event of second primary cancers. Table 21 and Table 22 present the results summary.

Table 22

Mean and Median Survival Time by BRCA1 Family History (n = 702)

Family status (n)	Mean	SD	Median	IQR
*BRCA*1 = 0 (219)	13.114	1.33	14.000	0.48
*BRCA*1 = 1 (483)	12.557	0.65	14.000	0.22
Overall (702)	12.731	0.54	14.000	0.22

Note. Estimation is limited to the largest survival time if it is censored

Table 23

Mean and Median Survival Time by BRCA2 Family History (n = 702)

Family status (n)	Mean	SD	Median	IQR
*BRCA*2 = 0 (201)	13.095	1.03	14.000	0.48
*BRCA*2 = 1 (501)	12.285	0.79	14.000	0.24
Overall (702)	12.731	0.54	14.000	0.22

Note. Estimation is limited to the largest survival time if it is censored

As Table 22 and Table 23 show, there are observed statistically significant differences in the relationship between both BRCA1 and BRCA2 family status and time to diagnosis of second primary cancers. Of importance, are the median time to event estimates for BRCA1 family status and BRCA2 family status at 95% CI are [13.89 - 14.11] and [13.88 - 14.12] respectively. The BRCA1 family status and BRCA2 family status have the same overall time to event estimate of 14.000 years. The log- rank test for BRCA1 family status was 14.116, with p = 0.000, while the log-rank test for BRCA2

family status was 11.359, with p = 0.001. Both BRCA1 family status and BRCA2 family status results are statistically significant.

Figure 11 and Figure 12 show the KM's survival curve of differences between BRCA1/BRCA2 family statuses and time to event of second primary cancers.

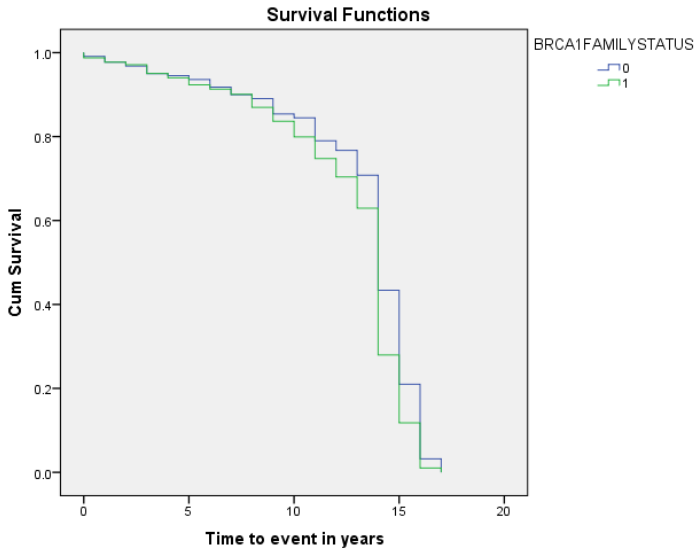

Figure 11. KM's survival curve of BRCA1 family status (p = 0.000)

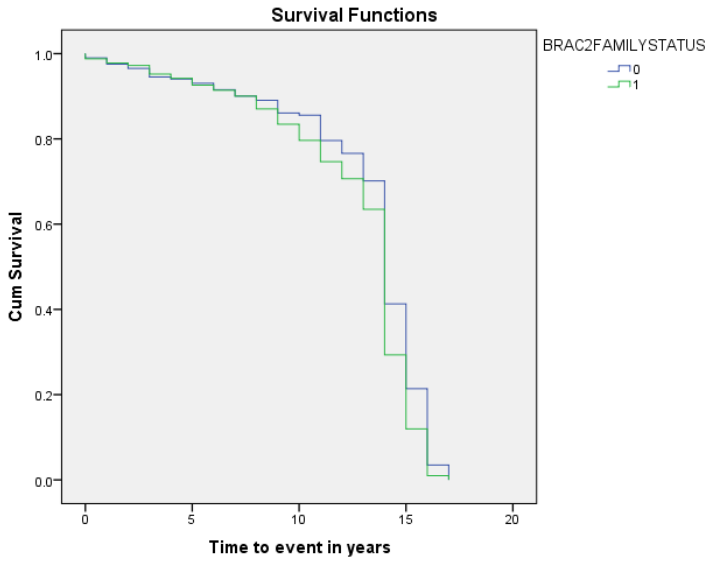

Figure 12. KM's survival curve of BRCA2 family status (p = 0.001)

Both BRCA1 and BRCA 2 family histories had 14 years for median estimated time to event.

Hazard ratio and the test of proportionality. I present the summary of a Cox regression conducted to determine the hazard ratio for smoking status, BRCA1 family status, and BRCA2 family status. I employed the composite endpoint (event) analysis due to the sparsity of events for the various second primary cancer sites. The hazard ratio generated will be the measure of association in this case. The hazard ratios of the covariates were determined and the assumption of proportional risks required to use CPH was also checked using the KM's curves.

Table 24 shows the Cox model for smoking status, BRCA1/BRCA2 family statuses sample with hazard ratios.

Table 24

Cox Hazard model for Smoking status, BRCA1, and BRCA2 Family status (n = 702)

Status (n)	Hazard ratio	95% Confidence interval
Smoking (302)	1.086	0.94, 1.26
*BRCA*1 Family status (483)	1.193	0.95, 1.51
*BRCA*2 Family status (501	1.086	0.86, 1.38

In Table 24, the hazard ratios at 95% CI risk ratio for smoking status is not statistically significant [0.94 – 1.26]. BRCA1 and BRCA2 family statuses are not also statistically significant, as shown with the 95% CIs risk ratio (B) [0.94 – 1.26], [0.95 – 1.51], and [0.86 – 1.38] respectively. This means that over 16 years of follow-up, the hazard for second primary cancers risk among patients who smoked was 10.9 times higher than those not diagnosed with breast cancer. Consequently, over 16 years of follow-up, the hazard for second primary cancers risk among BRCA1 family status and BRCA2 family status are 11.9 times and 10.9 times higher respectively in the population than those not diagnosed with breast cancer. The hazard ratio by smoking status, BRCA1 family status, and BRCA2 family status were determined and the test of proportionality was ascertained using the Kaplan-Meier curves. The Kaplan-Meier curves showed hazards are proportional within the groups. The CPH assumption was met.

Summary

In this chapter, I examined the risks of diagnosis of second primary cancers including colorectal, endometrial, cervical, kidney, thyroid, and bladder among women who had been diagnosed with breast cancer using the composite endpoint method by

employing data from the Breast Cancer Family Registries. Three risk factors, *BRCA* gene mutation status (BRCA1, BRCA2 and BRCA both 1 and 2), race/ethnicity, and age at diagnosis (NCI, 2015) were used to answer the research questions. The role of confounder and interaction between the covariates, smoking, and BRCA1/BRCA2 family status were also examined. As observed in this study, all of my findings associated with the two research questions and covariates suggest that it is possible to predict the risk of diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer. In KM's analysis, I identified the overall median time to event of second primary cancers to be 14 years. In the inferential multivariate Cox proportional hazard regression model, I also identified BRCA2 gene mutation and race/ethnicity as significant risk factors for diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer.

In Chapter 5, I summarize, analyze, and interpret key findings from these results and discuss whether they confirm, disconfirm, or extend existing knowledge per the literature review and the conceptual framework for this study. I also acknowledge and discuss the limitations of the study in terms of generalizability and/or trustworthiness, validity, and reliability. Recommendations for further research grounded in the strengths and limitations of the study and the literature reviewed in chapter 2 will be suggested, specifically as related to BRCA testing in the various communities and locations with the BCFR sites in the United States, Canada, and Australia. In this context, implications for

positive social change and recommendations for practice will be discussed, along with methodological, theoretical, and/or empirical implications. Finally, conclusions will be drawn to capture the key essence of the study.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

There are limited data on risk factors of BRCA1/BRCA2 gene mutations and risk of diagnosis of second cancers after breast cancer diagnosis among varying age, gender, and racial and ethnic groups in the United States. The role of age and ethnicity in diagnosis of BRCA-related cancers has been investigated (Al-Mulla et al., 2009; Jemals et al., 2003), but needs further clarification. There are data indicating that the risk for developing a second cancer may be significant for patients already diagnosed with breast cancer (Lee et al., 2008; Lee et al., 2006). The purpose of this quantitative study was to examine whether a relationship exist between BRCA gene mutations, ethnicity, age and gender, and risk of diagnosis of second primary cancers, including colorectal, endometrial, cervical, kidney, thyroid, and bladder cancer, among women diagnosed with breast cancer. Previous scholars observed a shared relationship with BRCA gene mutations and second primary cancers (Mocci et al., 2013; Kadouri et al., 2007). Mocci et al. (2013) observed that the women diagnosed with a BRCA-mutation-related breast cancer before 50 years of age were at a higher risk for developing a second cancer. The premise of this study was based on empirical findings that certain subsets of breast

cancer patients have demonstrated an elevated risk of developing second primary cancers (Kmet et al., 2003; Youlden & Baade, 2011).

According to the findings of this study, the overall median time to event of second primary cancer, colorectal, endometrial, cervical, kidney, thyroid, or bladder among women with BRCA-related breast cancer was 14 years. The log-rank test of the three BRCA mutation status did not show any statistical significance (BRCA1 = 0.797, with p = 0.372; BRCA2 = 1.808, with p = 0.179; and BRCA both 1 and 2 = 0.001, with p = 0.972). The multivariate CPH analysis hazard ratio for BRCA1 mutation was 0.781, p = 0.234, while the BRCA both 1 and 2 mutation hazard ratio was 0.891, with p = 0.667. I found no relationship between BRCA1 and risk of diagnosis of second primary cancers. I also found no relationship between BRCA both 1 and 2 and risk of diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer. Similarly, race/ethnicity had an overall time to event of 14 years. The log-rank test of equality showed 29.482 with a corresponding p = 0.000. The hazard ratios for White (includes the Ashkenazi Jews) and American I/H at 95% CIs hazard ratio [1.17 – 1.93] and [1.12 – 1.81] showed a relationship between race/ethnicity and risk of diagnosis of second cancers, while the hazard ratio for Black did not show any relationship [0.742 – 1.730]. The overall median time to event estimates of age groups <46 years, 47-56 years, and 57 years and older was 14 years. The Spearman correlation coefficient r_s = 0.026. The hazard ratios for <46 years and 47-56 years at 95% CIs [0.76 – 1.17] and [0.76 – 1.13] did not demonstrate a relationship between age groups and risk of

diagnosis of second primary cancers among women with BRCA-related breast cancer. Similarly, the three study covariates, smoking status, BRCA1 family status, and BRCA2 family status, had overall median time to event of 14 years. The log-rank test for smoking status was 1.844, and $p = 0.174$, while the log-rank test for BRCA1 family status was 14.116, with $p = 0.000$. The log-rank test for BRCA2 family status was 11.359, with $p = 0.001$. None of the covariates showed a positive relationship with risk of diagnosis of second primary cancers. The hazard ratio at 95% CI of smoking status was [0.94 – 1.26]. The 95% CI hazard ratios of BRCA1 and BRCA2 family statuses at 95% CI were [0.94 – 1.26], [0.95 – 1.51] and [0.86 – 1.38] respectively.

In Chapter 5, I begin with a brief review of the second primary cancers and various relationships with the predictor variables, BRCA gene mutation status, that relate to my first cohort and first research question and race/ethnicity and age at diagnosis that relate to my second cohort and research question. I follow this with a comprehensive interpretation of the findings as they relate to existing literature, my theoretical framework, and the study population. I present the limitations of the study in terms of generalizability and/or trustworthiness, validity, and reliability. Finally, I provide recommendations for further research and discuss the implications for social change based on my research conclusions.

Interpretation of the Findings

I conducted a prospective cohort study using 702 patients with breast cancer from the NCI-BCFR database to determine if there was a relationship between the risk of

diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, and the independent variables of BRCA status, race/ethnicity, and age at diagnosis. The relationship between the dependent variable and study covariates BRCA1 family history/BRCA2 family history was also examined. Composite endpoints approach was used in defining events and testing the stated associations. The study participants and controls were then used to ascertain the extent and significance of associations between the risk of diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder and the independent variables of BRCA status, race/ethnicity, and age at diagnosis. Direct relationships were observed between the risk of diagnosis of second primary cancers and BRCA2 and race/ethnicity. There was no relationship between risk of diagnosis of second primary cancers and BRCA1, BRCA both 1 and 2, and age groups. I found no statistically significant association between risk of diagnosis of second primary cancers and covariates BRCA1 family history/BRCA2 family history.

Demographics

The variables I examined in this study included BRCA gene mutation status (BRCA1, BRCA2, and BRCA both 1 and 2), race/ethnicity (White, Black, American I/H and Asian), age groups (<46 years, 47-56 years, and 57 years and older), smoking, BRCA1/ BRCA2 family history, and time to event of second primary cancers (colorectal, endometrial, cervical, kidney, thyroid, and bladder). The descriptive statistics for each of these variables (Table 7) was computed. Frequencies were used to describe the

dichotomous and categorical variables, while mean and standard deviation were used for the continuous variables time to event as well as age in a noncategorical form.

BRCA status. In my study, BRCA1 and BRCA2 referred to BRCA gene mutations that are correlated with a high risk of breast and other cancers. BRCA both 1 and 2 refers to individuals diagnosed with both BRCA1 and BRCA2 gene mutations. In another study on BRCA1/2 founder mutations in Southern Chinese breast cancer patients, Kwong et al. (2012) observed the frequency of 69 (15.3%) deleterious BRCA mutations, comprising 29 in BRCA1 and 40 in BRCA2 out of the 451 probands analyzed. I computed and organized descriptive statistics for the BRCA status categorical variable (BRCA1, BRCA2, and BRCA both 1 and 2). About 67% of all the study subjects I investigated had one or two of the BRCA gene mutations after the initial diagnosis of breast cancer. I observed the highest frequency of BRCA gene mutation-related breast cancer status was for BRCA2 at 76.8%, followed by BRCA1 cases at 75.2%; 71.2% of subjects/cases had both BRCA1 and BRCA2 mutations. These results are similar to the findings of John et al. (2011) in which the BRCA1 mutation frequency in non-Hispanic White is much higher than the observed frequency in African Americans (Blacks) in the population (Table 8). However, I did not analyze frameshift mutations. Similarly, my study was consistent with Kwong et al.'s (2012) report of higher frequency of BRCA2 mutations than BRCA1 mutations in the study population. However, I did not use DNA sequencing such as was used in Kwong et al. study. Petrucelli et al. (2011) inferred that prognosis for BRCA1/2-related second cancers other than breast cancer depended on the

stage at which the cancer is diagnosed. In my review of the literature, I did not find many studies on BRCA both 1 and 2 mutations and their association with second primary cancer diagnosis (Petrucelli et al., 2011). Due to this limited literature, I investigated the relationship between BRCA both 1 and 2 gene mutations and time to diagnosis of second primary cancers (colorectal cancer, endometrial, cervical, kidney, thyroid, and bladder) among patients with BRCA-related breast cancers.

Race/ethnicity. Four distinct races/ethnicities were examined in this study: White (including the Ashkenazi Jews), Black, American Indian/Hawaiian, and Asian (including Chinese, Filipinos, Japanese, and Korean). My use of data from six BCFR sites, in different countries and geographic locations, was intended to ensure ethnic and racial diversity among study subjects. Several researchers have suggested that the prevalence of harmful BRCA1 and BRCA2 mutations may be different among individual ethnic and racial groups in the United States (Bougie & Weberpals, 2011; John et al., 2011; Malone et al., 2006). Malone et. al. (2006) found that BRCA1 mutations were significantly more common in White (2.9%) versus Black (1.4%) cases and in Jewish (10.2%) versus non-Jewish (2.0%) cases; BRCA2 mutations were slightly more frequent in Black (2.6%) versus White (2.1%) cases. I computed and organized descriptive statistics for race/ethnicity categorical variable into White, Black, American I/H, and Asian. John et al. (2011) found that non-Hispanic White patients had increased frequencies of BRCA1 frameshift gene mutations compared to the African Americans. John et al. noted that the non-Hispanic White study population diagnosed with BRCA1 mutations showed 36%

mutations, whereas in African Americans, 25% of BRCA1 mutations were identified. In my study, I had similar observations with White participants (78%), followed by Asian (10.8%), Black (10.1%), and American I/H (0.06%). Conversely, my findings did not align w Malone et al.'s (2006) that the prevalence of BRCA2 mutations related to breast cancer is highest in Blacks compared to the White cases in the study population. The high number of White paricipants in my study probably reflects the demographics of the communities in which the six BCFR sites are located. Therefore, the generalizability of my study result might be limited to the BCFR sites and various populations recruited for the study.

Age. I defined age in my study as the initial age at diagnosis of breast cancer among the study participants. I organized and computed descriptive statistics of age at diagnosis into categorical (age groups) from the initial continuous form. The frequency for study subjects were <46 years = 136 (19.4%), 47-56 years = 196 (26.9%), and 57 years and older = 370 (52.7%). For age in a continuous form, the median age of my study participants (702) was 57 years, with mean age = 57.07 and standard deviation of 11.118, positioning the average study subject in the midyears of life. This corroborates with the findings of Nussbaum et al. (2007) and Singletary et al. (2004) who found that most cancers of the breast occur after 50 years of age. Similarly, my study age demographics were in conformity with Beineret al.'s (2007) findings of diagnosis of endometrial cancer among women with BRCA1- or BRCA2-related breast cancer, aged 45 to 70. In contrast,

Papelard et al. (2000) and Sing et al. (2000) found that BRCA1 and BRCA2-mutation-related breast cancer develops often before 50 years of age.

Time to event. In this study, time to event was presented as the time it takes for a patient with a BRCA1- or BRCA2-mutation-related breast cancer to be diagnosed with another form of cancer. For this study, I organized and calculated the time to event descriptive statistics as a continuous variable. For the study cohort, the mean time to event of second primary cancers among women diagnosed with BRCA-related breast cancer was 12.73, with a standard deviation of 3.642; the median time to event was 14 years with inter quartile range of 0.2 My study results are consistent with Youlden and Baade's (2011) findings**.** Youlden and Baade observed that one in every 10 (10.6%) of the second primary cancers were diagnosed within a year of the first diagnosis and more than one in five (20.6%) were diagnosed at least 10 years afterwards. While both studies examined the same cancer sites, colon/rectum, endometrium, cervix, kidney, thyroid and bladder, the Youlden and Baade study differed from mine because they estimated various years of second cancers diagnosis after initial breast cancer, and they did not indicate if the female study participants had BRCA gene mutation diagnosis.

Smoking. Smoking is a known risk factor for breast cancer (Leet al., 2011). The latest American Cancer Society study on smoking and association with breast cancer reported an increased frequency pertaining to the risk of breast cancer among smokers compared to nonsmokers (American Cancer Society, 2013). The American Cancer Society, (2013) reported that 24% higher cases of breast cancer among women smokers

than in nonsmokers and 13% higher in former women smokers than in nonsmokers. However, smoking is not known to be a risk factor for BRCA1 and BRCA2 germline pathogenic variant-related breast cancer (Ginsberg et al., 2009). My descriptive statistics suggested that 42% of my study participants had a history of smoking. The relatively low percentage of smokers in my study seems to be consistent with Ginsberg et al.'s (2009) findings that it is likely that non-BRCA-related breast cancer is occurring by a different, environmental mechanism, which may involve carcinogenic exposure.

BRCA1/BRCA2 family history. In my study, BRCA1 and BRCA2 family history referred to BRCA1 or BRCA2 gene mutations diagnosed from an individual with a history of a close family member previously diagnosed with either gene mutation. The influence of family history in BRCA1 and BRCA2 gene mutation carriers and increased risk of breast and other cancers remains unclear (Metcalfe et al., 2010). Metcalfe et al. (2010) reported a 18.1% in a 10-year cumulative risk of breast cancer for BRCA1 and 15.2% for BRCA2 in a multinational cohort consisting of 3,011 women with BRCA1 or BRCA2 mutations who were followed up for a mean of 3.9 years, during which time 243 incident breast or other cancers were recorded. Further, Metcalfe et al. observed that the risk of breast cancer increased by 1.2-fold for each first-degree relative with breast cancer before age 50 years. In the BCFR cohort recruited for this study, 68.8% of my study participants reported a family history of a BRCA1 gene mutation, while 71.4% reported family history of a BRCA2 gene mutation. My result was not consistent with the findings of Metcalfe et al. who reported a higher percentage (18.1%) for BRCA1 mutation carriers

and lower percentage (15.2%) for BRCA2 gene mutation carriers. However, my study population differred from that of Metcalfe et al., and this difference may have influenced the results.

Research Question 1

My first research question was aimed at the relationship between the dependent variable, time to diagnosis of second primary cancers (colorectal, endometrial, cervical, kidney, thyroid, and bladder) and the independent variable of BRCA gene mutation status.

Survival analysis. As shown in Tables 9, 10, and 11, after analyzing the relationship between breast cancer mutation genes, BRCA1, BRCA2, and BRCA both 1 and 2 and time to diagnosis of second primary cancers, I found the overall median time to diagnosis was 14 years. The log-rank test of equality for each of the three BRCA mutation statuses did not demonstrate a statistical significance (BRCA1 = 0.797, p = 0.372; BRCA2 = 1.808, p = 0.179, and BRCA both 1 and 2 = 0.001, p = 0.972). Similarly, after stratification of the breast cancer by BRCA status both 1 and 2 as shown in Table 12, the overall median time to diagnosis of a second primary cancer was 14 years. It may take an average of 14 years for a person with either or both of the BRCA gene mutations to be diagnosed with second primary cancers in the study population. Further, there was no relationship between BRCA1, BRCA2, and BRCA both 1 and 2 and time to diagnosis of second primary cancers (colorectal, endometrial, cervical, kidney, thyroid or bladder) among women with breast cancer. Similarly, after

stratification of breast cancer (without gene mutation) by BRCA both 1 and 2, the median time to diagnosis of second primary cancers remained 14 years. My study findings of no relationship between BRCA1, BRCA2, and BRCA both 1 and 2 and time to diagnosis of second primary cancers were not consistent with Mocci et al.'s (2013) study that applied survival analysis using the time in years from birth to diagnosis of pancreatic cancer after initial breast cancer diagnosis in a BCFR study cohort, likely because my study sample did not include women without the mutation as a comparison. Mocci et al. observed a relationship and increased risk of second primary pancreatic cancer diagnosis in BRCA-mutation-related breast cancer patients. Moreover, Mocci et al.'s study was not designed to study time to diagnosis of second primary cancers using the composite endpoints, but rather to examine the risk for developing second primary cancers.

Kaplan Meier analysis. The KM's survival curves confirmed my observations that the median time to event for BRCA1, BRCA2, and BRCA status both 1 and 2 were the same at 14 years respectively (Figures, 3, 4, and 5). Similarly, after stratification, the KM's survival curve suggested the median time to event of 14 years as demonstrated in Figures 6 and 7.

Cox Proportional Hazards model. I performed a Cox regression analysis to estimate the hazard ratio for the breast cancer gene mutations, BRCA1, BRCA2, and BRCA both 1 and 2. CPH provides hazard ratios, which are defined as an estimate of the ratio of the hazard rate in patients with BRCA and non-BRCA breast cancer (Table 13). The hazard rate represents the likelihood that if the event in question has not already

occurred, it is expected to occur in the next time interval, divided by the length of the interval (Spruance et al., 2004). KM curves were used to confirm the assumption of proportionality needed to use CPH.

BRCA1/ BRCA both 1 and 2. The hazard ratio associated with BRCA1 was 0.781 with CI [0.529 – 1.17]. This result is not statistically significant. This means that over 16 years of follow-up, the hazard for second primary cancers risk among patients diagnosed of BRCA1 gene mutations was 7.8 times higher than those not diagnosed with breast cancer. Further, my study result means there is no relationship between BRCA1 gene mutation and risk of diagnosis of second primary cancers when compared to BRCA2 mutations. The hazard ratio of BRCA both 1 and 2 was 0.891 with CI [0.53 – 1.50]. This is not a statistically significant result. This means that over 16 years of follow-up, the hazard for second primary cancers risk among patients diagnosed of BRCA1 gene mutations was 8.9 times higher than those not diagnosed with breast cancer. My study results also demonstrated no relationship between BRCA both 1 and 2 gene mutation and risk of diagnosis of second primary cancers. Therefore, I failed to reject the null hypothesis of no relationship between BRCA1/BRCA both 1 and 2 and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer. These findings are not consistent with the conclusion of Kadouri et al. (2007) that there is an association between BRCA gene mutations and diagnosis of second cancers. Kadouri et al. (2007) observed a 2.5-fold increase in any other cancer and a fourfold risk of colon cancer among BRCA1 carriers. The

corresponding hazard ratios in BRCA2 carriers were non-significant, except for the markedly elevated risk of lymphoma. Their findings suggest a role for BRCA1/2 mutations in colorectal cancer risk in a subgroup of breast cancer/ovarian cancer-affected carriers. None of the women with a BRCA2 mutation were diagnosed with uterine cancer. These data suggest that BRCA1 may be responsible for an increased risk of an aggressive form of uterine cancer, but there is insufficient data on the potential relationship to endometrial cancer. The study was not designed to look at time to diagnosis of second primary cancers in a population with breast cancer.

BRCA2. The hazard ratio associated with BRCA2 was 1.471 with CI [1.03 – 2.11]. This result is statistically significant. This means that over 16 years of follow-up, the hazard for second primary cancers risk among patients diagnosed of BRCA1 gene mutations was 14.7 times higher than those not diagnosed with breast cancer. Further, my study result means there is a relationship between BRCA2 gene mutation and risk of diagnosis of second primary cancers. Therefore, I rejected the null hypothesis of no relationship between BRCA2 and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, and bladder. This result confirms literature (Shu et al., 2014; Al-Mulla et al., 2009; Johannesdottir et al., 1996) regarding BRCA2 as a potential risk factor to diagnosis of second primary cancers. My research result goes further not only to determine the relationship between BRCA2 and second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer, but also examined the median time to event. The median time

to event as observed in all the BRCA gene mutation statuses and diagnosis of second primary cancers was 14 years. This provides additional insight pertaining to what was known previously about BRCA2 as a risk factor for second primary cancers among women diagnosed with breast cancer in susceptible populations.

Similarly, a recent study that used survival analysis CPH investigated the association between germline mutation in BRCA1 or BRCA2 and ten years of survival among women with epithelial ovarian cancer diagnosis (Candido-dos-Reis et al; 2015). Candido-dos-Reis and colleagues aim was to analyze the effect of germline mutations in BRCA1 and BRCA2 on mortality in patients with ovarian cancer up to 10 years after diagnosis. The researchers used unpublished survival time data for 2,242 patients from two case-control studies and extended survival time data for 4,314 patients from previously reported studies (Candido-dos-Reis et al., 2015). Survival time was analyzed for the combined data using CPH with BRCA1 and BRCA2 as time-varying covariates. Competing risks were analyzed using Fine and Gray model. The hazard ratio (HR) for *BRCA1* was 0.53 at time zero and increased over time becoming greater than one at 4.8 years. For BRCA2, the HR was 0.42 at time zero and increased over time (predicted to become greater than 1 at 10.5 years) (Candido-dos-Reis et al., 2015). Unlike my study, the above study mainly employed survival analysis in BRCA1 or BRCA2 and ten-year survival for women diagnosed with epithelial ovarian cancer. The researchers did not investigate other potential cancer sites and the time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women

with breast cancer. My study further extends knowledge in the discipline by using the KM's analysis and CPH model to examine relationship between several risk factors such as BRCA status, and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer. Therefore, in addition to the large risks of ovarian and breast cancers observed by Candido-dos Reis et al. (2015), my study finding confirms that BRCA2 may have a relationship with increased risk of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer in a susceptible population.

The conceptual framework for Research Question 1 was based on literature showing that certain subsets of BRCA related breast cancer patients may have demonstrated elevated risk of developing second primary cancers (Menes et al., 2015; Brose et al., 2002). Menes and colleagues followed 800 women diagnosed with breast cancer from the Breast Cancer Family Registry (BCFR) who were carriers of a BRCA1 or BRCA2 pathogenic mutation or a variant of unknown clinical significance and estimated the 10-year cumulative risk of second primary breast cancer including more testing information on family members (Menes et al., 2015). In addition, Brose et al. (2002) observed a two-fold increased risk of colon cancer, threefold risk of pancreatic cancer, fourfold risk of stomach cancer, and 120-fold increased risk of fallopian tube cancer among BRCA1 mutation carriers with breast cancer (Brose et al., 2003). In this study, I have shown that BRCA1 and BRCA both 1 and 2 gene mutations in breast cancer

patients may not be related to risk of diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder. This is a notable finding. I have also demonstrated that there is a positive association between BRCA2 gene mutation in breast cancer patients and risk of diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder. H_{01} was: There is no relationship between BRCA mutation status and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer. H_{A1} was: There is a relationship between BRCA mutation status and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer. Therefore, there was sufficient statistical rigor to assert the strength of no relationship between the BRCA1/BRCA both 1 and 2 gene mutations among patients with breast cancer and time to diagnosis of second primary cancers. In addition, there was also sufficient statistical rigor to assert the strength of a relationship between the BRCA2 gene mutation among patients with breast cancer and time to diagnosis of second primary cancers. There was also sufficient statistical power to maintain the negative associations between the presence of the BRCA1/BRCA both 1 and 2 gene mutations and BRCA2 positive association and second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder were not the result of chance alone. Thus, I failed to reject the null hypothesis of relationship between BRCA1/BRCA both 1 and 2 gene mutations and the time to diagnosis of second primary cancers. In addition, the null hypothesis of no relationship between BRCA2 gene mutation and time to diagnosis of second primary

cancers was rejected. This suggest there may not be any relationship between BRCA1/BRCA both 1 and 2 gene mutations status and risk of diagnosis of second primary cancers, and there may be a relationship between BRCA2 gene mutation and risk of diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among patients with breast cancer.

Research Question 2

My second research question aimed at the relationship between the dependent variable time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among patients with BRCA related breast cancer and the independent variables of race/ethnicity and age at diagnosis.

Survival analysis. I presented in Table 14, Table 15, Table 16 and Table 17 analyses of the relationship between race/ethnicity and age at diagnosis and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder among women with BRCA-related breast cancer. I observed that the overall median time to diagnosis of a second primary cancer was 14 years as observed in other variables. The log-rank test of equality for race/ethnicity showed statistical significance (race/ethnicity = 29.482, with p = 0.000). The Spearman correlation coefficient r_s for age groups did not demonstrate any statistical significance (r_s= 0.026, p = 0.487) as well as the Spearman correlation coefficient r_s for age in a continuous form (r_s= 0.018, p = 0.627). This means that it may take an average of 14 years for an individual of White, Black, American I/H or Asian race to be diagnosed with second primary cancers in the

study population. Further, there is a relationship between race/ethnicity and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid or bladder, among women with breast cancer. My result is consistent with the the observation of Al-Mulla et al. (2009) in their cohort study that used survival analysis and found a significant association in Yorkshire and Humberside, United Kingdom families with breast and/or ovarian cancer and BRCA1 or BRCA2 mutation and the occurrence of a second cancer including vaginal, colon, prostate, and pancreatic. My study differs from Al-Mulla et al. study in that my study involved many races/ethnicities whereas Al-Mulla et al. study only involved the White population. My study age groups as noted also in race/ethnicity variable presented an average time of 14 years for diagnosis of second primary cancers in the study population. Further, the age groups result also showed that there is no association between age groups and time to diagnosis of second primary cancers. This finding was not consistent with Al-Mulla et al. (2009) study that demonstrated a positive association between age at diagnosis (median age of 55 years) and second primary cancers among the study participants with BRCA1/BRCA2 related breast cancer. My study result may not be generalized in that it is limited to the data in the BCFR data set and the study population.

Kaplan Meier analysis. The KM's survival curves of race/ethnicities and age groups showed that the overall median time to event for race/ethnicity and age groups are the same at 14 years respectively as demonstrated in Figures 7 and 8.

Cox Proportional Hazards model. I performed a CPH analysis to estimate the hazard ratio for race/ethnicity and age groups. CPH provides hazard ratios, which are defined as an estimate of the ratio of the hazard rate in patients with different races/ethnicities (White, Black, American I/H, and Asian) and age groups as shown in Table 17. The hazard rate represents the likelihood that if the event in question has not already occurred, it is expected to occur in the next time interval, divided by the length of the interval (Spruance, Reid, & Samore, 2004). The KM's curves were used to confirm the assumption of proportionality.

Race/Ethnicity. The hazard ratios associated with race/ethnicity are White, 1.511 with CI [1.18 – 1.94], Black, 0.647 with CI [0.23 -1.67], and American I/H, 1.424 with CI [1.12 – 1.81]. This result is statistically significant for the White and American I/H races/ethnicities, but not statistically significant for Black race. There was no result generated for the Asian race/ethnicity. This implies that both White and American Indians and Hawaiians (though there are really too few of both to have any meaningful results that are significantly different), but that Blacks and Asians are not. Further, this means that over 16 years of follow-up, the hazard for second primary cancers risk among White and American I/H patients was 15.1 times and 14.2 times respectively higher than those not diagnosed with breast cancer. The results also mean that over 16 years of follow-up, the hazard for second primary cancers risk among Black race/ethnicity was 6.5%. Further, my study result means there is a relationship between race/ethnicity (White and American I/H) and risk of diagnosis of second primary cancers. The 95% CI

of Black race result demonstrated no relationship between race/ethnicity (Black and Asian, though Asian data was not generated after running the CPH as shown in Table 17) and risk of diagnosis of second primary cancers. Therefore, I rejected the null hypothesis of no relationship between race/ethnicity (White and American I/H) and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer. I also failed to reject the null hypothesis of no relationship between race/ethnicity (Black) and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer. My study result is consistent with the study of Al-Mulla et al. (2009) that noted an association between second primary cancers and BRCA1/BRCA2 related breast cancer in White English Yorkshire/Humberside population. Similarly, it is also consistent with Mocci et al. (2013) study that found a higher risk of developing a second primary cancer in White women with BRCA1/BRCA2 related breast cancer families from the breast cancer family registry. My study and Mocci et al. (2013) used the same BCFR database. A majority of the study participants were of the White race/ethnicity. The Mocci et al.'s study was limited in that it did not examine second primary cancer risk estimates based on a larger variety of ethnic groups.

Differences in race/ethnicity do, however, appear to affect the diagnosis of breast cancer and second primary cancers (Al-Mulla et al., 2009; Beiner et al., 2007).Few studies have been done that explored the relationship between Native-American and Hawaiian races/ethnicities and BRCA1/BRCA2 gene mutations as risk factors for breast

cancer. During this study, I did not locate any published article about American I/H and risk for second primary cancer diagnosis among women with BRCA- related breast cancer. According to Jardines et al. (2015), breast cancer risk is extremely low in American Indian (Native-American) women. Fred Hutch.org (2016) suggested that nationwide, American Indians and Alaska Natives generally have lower reported rates of cancer than all other racial groups, but those rates have been increasing in recent years, according to U.S. government data. In addition, these numbers may be underreported because of past flaws in collecting this information. However, of all racial and ethnic groups in the United States, American Indians and Alaska Natives have the poorest survival rates for all types of cancer combined (Fred Hutch.org, 2006). Death rates from breast cancer disease, however, were higher than Hispanics and Asian Americans/Pacific Islanders as reported by the NCI between 2002 and 2006 (Fred Hutch.org, 2016).

More research needs to be done in order to examine Native-American and Hawaiian women and associated risk for BRCA-related breast cancer in susceptible populations. My study provides additional insight by exploring various risk factors and time to diagnosis of second primary cancers, including colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with BRCA-related breast cancer. The fact that BRCA-related breast cancer is more common among the White race than the other races/ethnicities (Mocci et al., 2013; Dite et al., 2010; Neil et al., 2004; Thompson & Easton, 2002; Johannesdottir et al., 1996) supports my conclusion that second primary cancer may be dependent on BRCA-related breast cancer among susceptible racial/ethnic

populations. For these reasons, it is possible that the risk of diagnosis of second primary cancers may be confounded by race/ethnicity.

My result of no association between risk of diagnosis of second primary cancers and Black race seems to be consistent with the findings of Newman et al. (1998) and suggests that the incidence of BRCA mutations might be lower among breast cancer patients of African American ancestry. Newman et al. in their population-based study that included 99 women of African origin with breast cancer failed to find any disease related BRCA mutations in any of the women. Pal, Permuth-Wey, Holtje, and Sutphen (2004), had argued that sufficient empirical data may be helpful in estimating mutation risk among women of Black race/ethnicity. Further, my study finding of no association between risk of diagnosis of second primary cancers and Asian race/ethnicity was not consistent with Sing et al. (2000) who reported BRCA as a risk factor of second primary cancers among Asian populations with breast cancer. My study findings may have been impacted by the dominant White race (including the Ashkenazi Jews) among the study participants recruited from the various BCFR sites. Therefore, it may not be necessary to generalize my findings, because it is limited to the study population used for the study.

Age. The hazard ratios associated with age groups include <46 years at 95% CIs, 0.942 [0.76 – 1.17] and 47-56 years at 95% CIs, 0.925 [0.76 – 1.13]. These results are not statistically significant for any of the age groups. Further, these results failed to show an association between age groups and risk of diagnosis of second primary colorectal, endometrial, cervical, kidney, thyroid, or bladder cancers, among women with *BRCA*

related breast cancer. My study result was not consistent with Beiner et al. (2007) and Brose et al. (2002) who suggested age has an association with the diagnosis of second primary cancers. However, the gap between the association of second primary cancer diagnosis and age is dialogued with different study findings (Patrucelli, Daly, & Feldman, 2011; Al-Mulla et al., 2009). According to Patrucelli et al., there is no clear explanation presently for the observation that some individuals with a cancer-predisposing germline variant (BRCA1/BRCA2) may have multiple primary cancers before age 50 years, while others with the same cancer-predisposing germline variant may develop cancer only after age 70 years, or not at all. Younger age at diagnosis of BRCA related breast cancer have been proposed to show association with second primary cancers in a susceptible population (Mocci et al., 2013; Brose et al., 2002; Johannesdottir et al., 1996). Mocci et al. (2013) demonstrated that the women diagnosed with a BRCA mutation related breast cancer before 50 years of age were at a higher risk of developing a second cancer. The study was limited in that it examined only pancreatic cancer and no other second primary cancer risk estimate based on many ethnic groups. Additionally, Brose et al. (2002) investigated BRCA*1*-related cancer risks for individuals ascertained in a breast cancer risk evaluation clinic. Brose and colleagues found by age 70, female breast cancer risk was 72.8%, the risk for developing a second primary breast cancer by age 70 was 40.5%, a two-fold increased risk of colon cancer, threefold risk of pancreatic cancer, fourfold risk of stomach cancer, and 120-fold increased risk of fallopian tube cancer among *BRCA1* mutation carriers with breast cancer (Brose et al., 2002). Similarly,

a Taiwanese breast cancer population demonstrated the peak incidence of diagnosis of second cancer was among women in their 40s, with approximately 2% developing a non-breast second primary cancer, with an average survival time of 2.87 years after the second cancer diagnosis (Lee et al., 2008). Therefore, there remains a gap in the literature between association of age at diagnosis and time to diagnosis of second primary cancers among patients with BRCA-related breast cancer. My findings suggest that recognizing differences in age at diagnosis is important to developing the most appropriate screening and follow-up procedures.

The conceptual framework for Research Question 2 focused on the existing literature showing certain subsets of BRCA gene mutation related breast cancer patients may have demonstrated elevated risk of developing second primary cancers with race/ethnicity and age at diagnosis (Mocci et al., 2013; Brose et al., 2002). Al-Mulla et al. (2009) reported of identifying 14 new BRCA1/BRCA2 gene mutations among the Yorkshire/Humberside population and their association with second primary cancers. Similarly, Youlden & Baade (2011) found in a retrospective cohort study conducted in Queensland, Australia, that the highest proportion of second primary cancers occurred after initial diagnosis of female breast cancer (12.6%). The second primary cancers observed in their study included, pancreatic, colorectal, endometrial, cervical, thyroid, kidney, and bladder cancers (Youlden & Baade, 2011). This study did not assess BRCA status. Similarly, Kmet et al. (2003) found that incidence of colorectal cancer was associated with a family history of breast cancer, high body mass index and lobular breast

cancer histology. I have shown that race/ethnicity (White and American I/H) among BRCA gene mutation related breast cancer patients is associated with the risk to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder. My study did not show any association between Black and Asian races and the time to diagnosis of second cancers, among patients with BRCA-related breast cancer. These are important findings. I have also demonstrated that there is no positive association between age at diagnosis among BRCA gene mutation-related breast cancer patients and risk to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder. H_{A2a} was: There is a relationship between ethnicity and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, renal, thyroid, or bladder, among women with BRCA-related breast cancer. H_{02a} was: There is no relationship between ethnicity and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, renal, thyroid, or bladder, among women with BRCA-related breast cancer. The H_{02b} was: There is no relationship between age status and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, renal, thyroid, or bladder, among women with BRCA-related breast cancer. Therefore, there was sufficient statistical rigor to assert the strength of a positive relationship between race/ethnicity (White and American I/H) and time to diagnosis of second primary cancers, among women with BRCA-related breast cancer. There was also sufficient statistical rigor to maintain the negative associations between Black and Asian races, age at diagnosis and time to diagnosis of second primary cancers, among women with

BRCA-related breast cancer. In addition, there was also sufficient statistical power to maintain the positive associations between the presence of White and American I/H positive association, and age at diagnosis and second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder were not the result of chance alone. Thus, I rejected the null hypothesis of no relationship between race/ethnicity and the time to diagnosis of second primary cancers. In addition, the null hypothesis of no relationship between age at diagnosis and time to diagnosis of second primary cancers was not rejected. This suggests there may be a relationship between race/ethnicity and time to diagnosis of second primary cancers, and there may not be a relationship between age at diagnosis and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with BRCA-related breast cancer.

I presented in Table 21 and table 22 analyses of the relationship between smoking and BRCA1/BRCA2 family history and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder among women with BRCA-related breast cancer. I observed that the overall median time to diagnosis of a second primary cancer for smoking variable was 14 years as observed in other variables. The log-rank test for smoking status was 1.844, and $p = 0.174$ and did not show any statistical significance.

Similarly, BRCA1/BRCA2 family history presented an overall median time to event of 14 years. The log-rank test for BRCA1 family status was 14.116, with p =

0.000, while the log-rank test for BRCA2 family status was 11.359, with p = 0.001. Both BRCA1 family status and BRCA2 family history results are statistically significant.

This means that it may take an average of 14 years for an individual with a positive smoking history to be diagnosed with second primary cancers in the study population. The log-rank test result means, there is no relationship between smoking history and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid or bladder, among women with breast cancer. This result was not consistent with the observations of Le et al. (2011) and Ginsberg et al. (2009) that smoking is associated with breast cancer and also increases breast camcer risk in people diagnosed with BRCA1 or BRCA2 gene mutations. My study also noted in BRCA1/BRCA2 family history variables an average time of 14 years for diagnosis of second primary cancers in the study population. This means it may take an individual with BRCA1/BRCA2 family history an average of 14 years to be diagnosed with second primary cancer. The statistical significance of my result pertaining to BRCA1/BRCA2 family history show that there is a relationship between BRCA1/BRCA2 family history and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid or bladder, among women with breast cancer. My result is consistent with the the observation of Al-Mulla et al. (2009) cohort study that used survival analysis and found a significant association in Yorkshire and Humberside, United Kingdom families with breast and/or ovarian cancer and BRCA1 or BRCA2 mutation and the occurrence of a second cancer including vaginal, colon, prostate, and pancreatic. My study differs from

Al-Mulla et al. study in that my study involves BRCA1/BRCA2 family history from many countries, whereas the Al-Mulla et al. study only involved the United Kingdom families' population. My study result may not be generalized, in that it is limited to the data in the BCFR data set and the study population.

Kaplan Meier analysis. The KM's survival curves for smoking and BRCA1 and BRCA2 family history show that the overall median time to event for race/ethnicity and age groups are the same at 14 years respectively as demonstrated in Figures 9 and 10 and 11.

Cox Proportional Hazards model. I performed a CPH analysis to estimate the hazard ratio for smoking and BRCA1 and BRCA2 family history. CPH provides hazard ratios, which are defined as an estimate of the ratio of the hazard rate in patients with smoking history and BRCA1 and BRCA2 family history as shown in Table 23. The hazard rate represents the likelihood that if the event in question has not already occurred, it is expected to occur in the next time interval, divided by the length of the interval (Spruance, Reid, & Samore, 2004). The KM's curves were used to confirm the assumption of proportionality.

Smoking. The hazard ratio of smoking at 95% CI, was 1.086 [0.94 – 1.26]. This is not a statistically significant result. This result infers that participants with smoking history are less likely to be diagnosed with second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder. This means for over 16 years of follow-up, the hazard ratio for second primary cancers risk among smokers was 10.9

times higher than those not diagnosed with breast cancer. This finding did not confirm literature that smoking history is implicated as a risk factor of breast cancer and other cancers (Le et al; 2011; Le et al., 2006). Individuals that carry BRCA1 or BRCA2 gene mutations have increased risk of developing breast cancer (Ginsberg et al., 2009; Russo, 2002). However, smoking seems not to appear as a risk factor for BRCA1 and BRCA2 germline pathogenic variant related breast cancer (Ginsberg et al., 2009). It has also been hypothesized that smoking may even lower breast cancer risk among BRCA1 and BRCA2 gene mutation carriers (Greer & Whitcomb, 2007). The reduction in breast cancer incidence specific to BRCA*1* and BRCA2 mutation positive smokers was hypothesized to be associated with the effect that cigarette smoking has on estrogen levels. Cancer risk in BRCA1 and BRCA2 mutation carriers peaks at about age 40–45 years, when estrogen levels are still high before the majority of women experience menopause, and then declines, in contrast with the general population in which the risk steadily increases throughout the life course (Narod, 2001). I have demonstrated in this study that smoking among women diagnosed with BRCA gene mutation related breast cancer is not associated with risk of diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder. Further empirical studies are needed in order to draw a conclusion pertaining to the relationship between smoking and association with second cancers among women diagnosed with BRCA-related breast cancer. This will be useful for screening and early treatment for women who may be at risk in the affected population.

BRCA1/BRCA2 family history. My study multivariate CPH analyses showed the hazard ratios at 95% CI for BRCA1 family history = 1.193 [0.95 – 1.51] and BRCA2 family history = 1.086 [0.86 – 1.38]. This is not a statistically significant result. This result infers that over 16 years of follow-up, the hazard ratio for second primary cancers risk among women with BRCA1/BRCA2 family history were 11.9 times and 10.86 times respectively higher than those not diagnosed with breast cancer. My study CPH result corroborates the results of Niell, et al. (2004). Niell and colleagues genotyped a northern Israeli population for the BRCA1 187delAG, BRCA*1* 5385insC, and BRCA2 6174delT founder mutations. A family history of breast cancer in a female relatives was not associated with an increased risk of colorectal cancer, even after adjustment for the presence of a BRCA founder mutation. Ashkenazi BRCA founder mutations may not confer a strong high risk of colorectal cancer and do not seem to be risk factor for colorectal cancer in that population (Niell et al., 2004). On the contrary, my study finding is not consistent with Shih et al.'s (2000) study that examined BRCA1 and BRCA2 mutations in Breast Cancer Families with Multiple Primary Cancers and observed that BRCA1 and BRCA2 mutations were twice as common in the presence of a reported second non-ovarian cancer. Shih et al. (2000) in their cohort study that examined 98 women with BRCA1 and BRCA2 mutations in Breast Cancer Families with Multiple Primary Cancers noted fifteen families with colorectal cancer as the second primary, endometrial and cervical cancers were reported as the second primaries in eight families each, and thyroid cancers were reported in seven families. On the premise of these two

studies and my study result, it is clear that my study not only attempted to explore the relationship between BRCA1/BRCA2 family history and second primary cancers, but went further to examine the time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with BRCA-related breast cancer. More studies with larger sample size and families from diverse populations may be needed to examine the association between BRCA1/BRCA2 family status as risk factors and time to diagnosis of second primary cancers in susceptible populations. I have demonstrated in this study that there is not a positive association between BRCA1/BRCA2 family history and the time to diagnosis of second cancers, among patients with BRCA-related breast cancer. More studies with larger sample size and families from diverse populations may be needed to examine the association between BRCA1/BRCA2 family status as risk factors and time to diagnosis of second primary cancers in susceptible populations.

The conceptual framework of this study relied upon genetic fundamental principles and published empirical data that support a mechanism of action for BRCA gene mutations in breast and other cancers. Smoking is implicated as a risk factor for breast cancer and other cancers (Le et al., 2011; Le et al., 2006). Individuals that carry BRCA1 or BRCA2 gene mutations have increased risk of developing breast cancer (Ginsberg et al; 2009; Russo, 2002). BRCA1 or BRCA2 family his may serve as a risk factor of second primary cancer. There was little information in the literature regarding the length of time to the diagnosis of a second, primary, non-breast cancer after a BRCA

related breast cancer diagnosis. Therefore, I identified smoking history, BRCA1 and BRCA2 family history as important factors to examine pertaining to time to diagnosis of second primary cancers. The inclusion of colorectal, endometrial, cervical, kidney, thyroid, and bladder cancers as dependent variables were selected based on data availability.

Limitations of the Study

This study was limited to the data available in the dataset. One limitation of this study was the non-availability of data from all 50 states in the BCFR databases. Another potential limitation was inherent to the size of the dataset. I originally intended to analyze only pancreatic and colorectal cancer as second primary cancers, but due to insufficient sample size and inclusion criteria, no subjects with pancreatic cancer were included. I used two cohorts instead of the initial intended three cohorts to answer my research questions. Unfortunately, no gender comparison was done because no male data was observed in the BCFR data set used. Here, gender may have served as a potential unmeasurable confounder because only the female gender was used for this study. In this study, the use of composite endpoints approach was used in defining events. Maybe a different result would have been observed if the events were analyzed individually based on the second primary sites studied. Despite composite end points may increase the study statistical power due to increase of the event rate, they may mislead if composite end points are of widely differing importance to patients, the number of events in the components of greater importance is small, and the magnitude of effect differs

considerably across components (Montori et al; 2005). Another potential limitation of using the composite endpoint in assessing risk is that if the study variable components are unreasonably combined or inconsistently defined, it may lead to inadequate reporting of result (The University of Texas Health Science Center, 2016). Further, not all family registry participants provided a blood sample for BRCA gene mutation testing, thus raising concern about potential selection bias. Recall bias related to family history may impact responses provided by the study participants when completing the questionnaire. Further, analyses of relationships among variables were limited by what information that were collected originally. It was not possible for me to gain additional information about the subjects in the cohorts, such as other genetic or non-genetic risk factors. This lack of information on women without the BRCA gene mutation may have limited a comparative analysis with those diagnosed with the BRCA gene mutation. My study findings may not be generalized because they are based on the BCFR data set used for the study and the study population.

Recommendations for Further Research

The NCI-BCFR database included registry data from three countries: Australia, Canada, and the United States. Four out of the six sites are located in the United States (California, New York, Pennsylvania, and Utah). Future studies could benefit from examining other geographical regions, to further elucidate the relationship between different risk factors and time to diagnosis of second primary cancers among women with BRCA-related breast cancer. Future studies that examine BRCA mutations and second

primary cancers in different populations could also look at potentially important confounders for cancer, such as gender, nutritional status, other genes, or radiation therapy status. Alternative study methodologies, such as a mixed method study design may provide additional information on factors that influence the time to diagnosis, such as attitudes and beliefs of clinicians and breast cancer patients regarding screening for second primary cancers. The findings of the study have potential implications to recommend for early screening for second primary cancers in high-risk breast cancer families.

Implications for Social Change

This study advanced the understanding of the relationship between BRC*A* gene mutations and time to diagnosis of second primary colorectal, endometrial, cervical, kidney, thyroid, and bladder cancer among women with breast cancer. The importance of early detection of a second cancer in this population is undeniable and has implications for treatment and recovery. My result finding of positive association between BRCA2 gene mutation and risk of diagnosis of second primary cancers and also between ethnicity and time to diagnosis of second primary cancers will be helpful to clinicians by providing early screening/testing for second cancers among women in the susceptible populations. Prophylactic surgery, which may occur before cancer is detected, remains an option for women who carry BRCA1 and BRCA2 mutations. This is usually done by surgically removing as much "tissue at risk" as possible with the option of bilateral mastectomy (removal of both breasts) (NCI, 2012). However, this approach may not be practical for

non-breast cancer. Chemoprevention has been used extensively in delaying the recurrence and reducing risk of cancer. Chemoprevention therapy involves the use of drugs, vitamins and other agents in cancer treatment (NCI, 2014). Understanding the factors associated with time to development of a second cancer allows for more and better options to be determined.

In this study, the overall median time to event for diagnosis of a second primary colorectal, endometrial, cervical, kidney, thyroid, or bladder cancer among women who had been diagnosed with breast cancer was 14 years. Race/ethnicity as a risk factor also shows White and American I/H have increased likelihood of being diagnosed with second primary cancers compared to other races in the study population. Thus, for over 16 years of follow-up, the risk for second primary cancers among White and American I/H races diagnosed with BRCA gene mutation related breast cancer were 15.1 times and 14.2times respectively higher than those not diagnosed with breast cancer. These data provide important information for health care providers of patients with BRCA mutations, to know better who is at risk for a second cancer and how long it may take to develop. Further, data on risk factors for development of second cancers would allow for identification of appropriate and timely screening procedures, determining the best course of action for prevention and treatment, and improving quality of life among breast cancer survivors.

Conclusion

The risk of second primary cancers has been observed among women after initial diagnosis of BRCA gene mutation related breast cancer. There is substantial evidence that BRCA gene mutations are associated with a variety of cancers, including new cancers that occur after a diagnosis of breast cancer. This study filled a gap in the literature on time to diagnosis of second primary cancers after initial diagnosis with a BRCA related breast cancer using the composite endpoint approach. Early detection of cancer remains one of the most valuable interventions to improve health outcomes. A greater understanding of the risk factors for the development of a second primary cancer and the length of time to development of a second primary cancer will allow for positive social change through a reduction in morbidity and mortality among women with breast cancer. I found the hazard ratios (HRs) for BRCA2 = 1.47, 95% CI [1.03 – 2.11], White = 1.511, 95% CI [1.18 – 1.94], and American I/H = 1.424, 95% CI [1.12 – 1.81] showed a positive association with time to diagnosis of second primary colorectal, endometrial, cervical, kidney, thyroid, and bladder cancers. These data provide useful information for risk assessment and therapy strategies, allowing clinicians to develop the most useful strategies for their breast cancer patients.

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Appendix A: Summary of the Results

Summary of Findings of Research Questions 1 and 2, Confounder, and Covariates

Research question 1	*Statistical results*	*Conclusions*
RQ1a: Is there a relationship between BRCA1 and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer?	*Kaplan-Meier overall median time to event = 14.000 years* *Log-rank test p-value = 0.797* *Cox Proportional Hazard (CPH) analysis* *Hazard ratio =0.781* *95% Confidence Interval [0.53 – 1.74]*	*Based on the CPH model, I will fail to reject the null hypothesis of no relationship between BRCA1 and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid or bladder, among women with breast cancer.*
RQ1b: Is there a relationship between BRCA2 and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer?	*Kaplan-Meier overall median time to event = 14.000 years* *Log-rank test p-value = 0.179* *Cox Proportional Hazard analysis* *Hazard ratio =1.471* *95% Confidence Interval [1.03 – 1.50]*	*Based on the CPH model I am able to reject the null hypothesis of no relationship between BRCA2 and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer.*
RQ1c: Is there a relationship between BRCA both 1 and 2 mutation status and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial,	*Kaplan-Meier overall median time to event = 14.000 years* *Log-rank test p-value = 0.972* *Cox Proportional Hazard analysis* *Hazard ratio = 0.981* *95% Confidence Interval [0.53 – 1.50]*	*Based on the CPH model, I will fail to reject the null hypothesis of no relationship between BRCA both 1 and 2 and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer.*

cervical, kidney, thyroid, or bladder, among women with breast cancer?	*Kaplan-Meier overall median time to event = 14.000 years* *Log-rank test p-value = 0.003*	*Based on the Log-rank test of equality, after the stratification, the result is statistically significant.*
		continue
	Statistical Results	*Conclusion*
Stratification of breast cancer by BRCA both 1 and 2	*Kaplan-Meier overall median time to event = 14.000 years* *White = 14.000 years* *Black = 11.000 years* *American I/H = 15.000 years* *Asian = 12.000 years* *Log-rank test for race/ethnicity p-value = 0.000*	
Research Question 2		
RQ2a: Is there a relationship between ethnicity and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, renal, thyroid, or bladder, among women with breast cancer?	*Cox Proportional Hazard analysis* *White Hazard ratio = 1.511* *95% Confidence Interval [1.18 – 1.94]* *Black Hazard ratio = 0.647* *95% Confidence Interval [0.23 – 167]* *American I/H Hazard ratio = 1.424* *95% Confidence Interval [1.12 – 1.81]*	*Based on the CPH model, I will reject the null hypothesis of no relationship between ethnicity (White and American I/H) and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer. I will fail to reject the null hypothesis of no relationship between ethnicity (Black) and time to diagnosis Of second primary Cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer.*

RQ2b: Is there a relationship between age status and time to diagnosis of second primary cancers, pancreatic, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women breast cancer?	*Kaplan-Meier overall median time to event = 14 years* *Spearman Correlation test* *p- value = 0.487* *Cox Proportional Hazard analysis* *< 46 years Hazard ratio = 0.942* *95% Confidence Interval* *[0.53 – 1.50]* *47-56 years Hazard ratio = 0.925* *95% Confidence Interval* *[0.76 – 1.13*	*Based on the CPH model, I will fail to reject the null hypothesis of no relationship between age and time to diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder, among women with breast cancer.*
		continue
	Statistical results	*Conclusion*
Adjusting for confounder and Covariates		
Confounder		
In RQ2a, I presented that race/ethnicity was a confounder. In order to further examine this, I evaluated BRCA status using the confounder in the analysis. I reevaluated the relationship between BRCA gene mutations (BRCA1, BRCA2, and BRCA both 1	*Cox Proportional Hazard analysis* *White Hazard ratio = 1.559* *95% CI = [1.21 -2.01]* *Black Hazard ratio = 0.673* *95% CI = [0.25 -1.80]* *American I/H Hazard ratio =1.476* *95% CI = [1.16 – 1.87]* *BRCA1 Hazard ratio = 0.867* *95% CI = [0.73 – 1.04]*	*Based on the CPH Models observed, race/ethnicity as a confounder may have a relationship with diagnosis of second primary cancers, colorectal, endometrial, cervical, kidney, thyroid, or bladder in the population of women with BRCA related breast cancer*

and 2) and White to American I/H race by conducting multivariate test (CPH) to see if there could be a difference		
Race/ethnicity and BRCA2	*White Hazard ratio = 1.895* *95% CI = [1.16 -1.92]* *Black Hazard ratio = 0.642* *95% CI = [0.24 -1.72]* *American I/H Hazard ratio =1.414* *95% CI = [1.12 – 1.81]* *BRCA2 Hazard ratio = 1.025* *95% CI = [0.86 – 1.23]*	
Race/ethnicity and BRCA both 1 and 2	*White Hazard ratio = 1.537* *95% CI = [1.19 -1.98]* *Black Hazard ratio = 0.664* *95% CI = [0.25 -1.78]* *American I/H Hazard ratio =1.459* *95% CI = [1.14 – 1.87]* *BRCA2 Hazard ratio = 0.925* *95% CI = [0.78 – 1.10]*	
Covariates		
Smoking	*Kaplan-Meier overall median time to event = 14.000 years* *Log-rank test p- value = 0.174* *Cox Proportional Hazard analysis* *Hazard Ratio = 1.086* *95% CI = [0.94 -1.26]*	*Based on the CPH model observed, the result is not statistically significant.*
BRCA1 family status	*Kaplan-Meier overall median time to event = 14.000 years* *Log-rank test p- value = 0.000* *Cox Proportional Hazard analysis* *Hazard Ratio = 1.193* *95% CI = [0.95 -1.51]*	*Based on the CPH model observed, the result is not statistically significant.*

BRCA 2 family status	*Kaplan-Meier overall median time to event = 14.000 years* *Log-rank test p- value = 0.001* *Cox Proportional Hazard analysis* *Hazard Ratio = 1.086* *95% CI = [0.86 -1.38]*	*Based on the CPH model observed, the result is not statistically significant.*