The Global Profile of Breast Cancer: Exploring the Disease Epidemiology Among International & Migrant Populations

by

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To my family:

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Chapter 1

Introduction

1.1: Significance

Breast cancer is the single greatest cancer killer among women across the globe [1-3]. Incidence rates of breast cancer are generally higher in developed regions of the world and lower in developing regions [3] (Figure 1.1). However, considerable increases in breast cancer incidence in developing areas of the world are expected due particularly to consistent international trends of younger age at menarche, smaller family size, and increasing body weight at postmenopausal ages, [4]. Furthermore, although the incidence of breast cancer may be lower in the developing world, the sheer number of people living in these areas means that the overall burden of cancer in this part of the world is high [5]. Understanding trends in breast cancer occurrence in settings with limited resources is especially critical for cancer control and planning efforts.

Inflammatory breast cancer (IBC) is an aggressive form of breast cancer with largely unknown etiology and a generally poor outcome [6]. An apparent heterogeneous global distribution in IBC occurrence has been reported, with a higher proportion of IBC out of all breast cancers in several regions within North Africa as compared to the United

States [6-11]. However, the literature in the field on IBC is extremely limited due to the rare nature of the disease and the lack of standardization in the diagnosis and registration of cases.

By evaluating trends in breast cancer from a global perspective and assessing breast cancer disparities by race and ethnicity, we can better understand the etiology of this complex disease, which may lead to better prevention strategies in the future. Furthermore, global trends and comparative studies of breast cancer are important to consider in order to promote the identification of risk factors which may be unrecognized when studies focus within populations with low levels of exposure risk factors.

Given the lack of comparative studies on breast cancer and IBC on a global scale, this dissertation investigated trends in breast cancer in a developing country at an important transition in westernization, one that is occurring in many other countries throughout the world. This research is critical for cancer control and planning efforts and it may also provide insight into the etiology of this heterogeneous disease. Additionally, this dissertation evaluated IBC among different racial and ethnic categories, including Arab Americans in the United States in order to understand potential disparities in occurrence and survival and to hypothesize reasons for these disparities. By investigating the occurrence of IBC among Arab Americans, this research adds to our limited knowledge of this disease among this important minority group. Finally, this research focused on the lack of standardization in IBC diagnosis by comparing differing criteria for diagnosis to demonstrate the effect of estimating IBC occurrence based on differing criteria. This study also provided concrete evidence of global heterogeneity in IBC occurrence, by utilizing the exact same criteria to identify IBC cases in both the United

States and in Egypt. Data from the Gharbiah population-based cancer registry in Tanta, Egypt, the Surveillance, Epidemiology and End Results (SEER) registry data from Detroit, New Jersey and California and breast cancer records from a single institution in Detroit, Michigan, which feeds cases to the Detroit SEER registry were utilized to conduct this research.

In summary, this research tackles an important global health issue of the rising risk of chronic diseases around the world and contributes concrete scientific evidence on the global occurrence of breast cancer in order to reduce the burden of this disease. This dissertation contributes meaningful and clinically-relevant knowledge to the emerging fields of international cancer epidemiology and translational research, while addressing global health and social inequities.

1.2: Background

Global breast cancer trends

According to the American Cancer Society, cancer is the world's top "economic killer" as well as its leading cause of death, and cancer costs more in productivity and lost life than AIDS, malaria, the flu and other diseases that spread person-to-person [12]. Cancer incidence is rising around the world due to population growth, aging, the impact of changes in behavioral risk factors and reduced mortality from infectious diseases. The developing world may be ill-prepared to deal with the consequences of cancer diagnosis both financially and socially. For example, there are only 84 radiation therapy centers, 256 radiation oncologists and 473 radiation technologists in all Arab countries, as compared with 1875, 3068 and 5155, respectively, in the USA, which has an equivalent

population of about 300 million [13]. Survival rates for certain cancers, such as cervical, breast and testicular, are directly related to country income [14] and more than 70% of all cancer deaths now occur in developing countries [15]. The lack of infrastructure and financial assets may lead to additional suffering associated with a cancer diagnosis, some of which could be avoided with increased resources. Therefore, the importance of studying cancer on a global scale has never been more critical.

Breast cancer incidence and mortality have been increasing in lower-income countries, which is attributed to changes in prevalence of reproductive risk factors, lifestyles changes and genetic and biological differences between ethnic and racial groups[16]. In Egypt, increasing breast cancer rates have been largely attributed to aging of the population, delay in time of first pregnancy, decrease in number of children and in breastfeeding, increase in use of external hormones, and a move toward high-calorie Western diets[16-19]. Although breast cancer incidence rates in Egypt are substantially lower than the rates in the United States and other developed countries [20-22], breast cancer is the most common cancer among women in Egypt, constituting 29% of National Cancer Institute cases in Cairo, Egypt [23]. The average age at diagnosis of breast cancer in Egypt is approximately a decade earlier than the age of diagnosis in Western countries [24]. This is likely due to the differences in the population structures between the countries, with a larger proportion of the Egyptian population in the younger age groups than in Western countries [25].

Inflammatory breast cancer

Inflammatory breast cancer (IBC) is the most aggressive and deadly form of breast cancer [26]. IBC diagnosis entails nearly twice the risk of death as compared to patients diagnosed with locally advanced breast cancer (LABC) [27,28]. IBC was first described by Sir Charles Bell in 1814 and was eventually termed inflammatory carcinoma of the breast by Lee and Tannebaum in 1924 [29,30]. Despite its name, IBC is not associated with an inflammatory response. The characteristic redness and swelling of the breast in IBC that superficially resembles inflammation are actually due to the lymph ducts that have been clogged with tumor cells, termed dermal lymphatic invasion [31,32] (Figure 1.2). Diagnosis of IBC is based on clinical symptoms (erythema, edema and peau d'orange) and pathologic characteristics (dermal invasion of breast lymphatic ducts) that are not uniformly observed among all patients with IBC. Therefore, by using a combination of the clinical and pathological criteria, IBC can be defined in different ways [33]. Epidemiologic research on IBC has been limited in part due to this differing criteria used for IBC diagnosis and the rare nature of the disease, which makes it difficult to obtain adequate representative samples of IBC cases.

Diagnosis of inflammatory breast cancer

Haagensen designated the clinical characteristics of IBC in 1956 to include rapid enlargement of the breast, generalized induration (hardening) with or without a distinct breast mass, acute redness or erythema involving at least one-third of the breast, heat, edema of the breast (peau d'orange), swelling and sometimes pain and tenderness within breast and axilla [34] (Figure 1.3). The constellation of these clinical characteristics distinguish IBC from neglected locally advanced breast cancer with skin involvement

[35]. One of the earliest changes associated with IBC is erythema, with the skin of the breast appearing pink and quickly progressing to dark red or purple and spreading diffusely over the entire breast. IBC is often associated with rapid breast enlargement resulting from edema caused by tumor blockage of the lymphatic vessels and may also be accompanied by a sensation of warmth. The term peau d'orange is used to describe the dimpled appearance of the breast in IBC, such that it emulates the skin of an orange. Nipple retraction may be present on examination of the affected breast. No discrete mass or tumor is palpable on clinical examination in about one third of patients with IBC [35].

There is a wide variation in symptom presentation in IBC and most of the clinical characteristics associated with IBC are nonspecific [36]. Several disease states including infectious mastitis, abscess, ductal estasia, congestive heart failure, other malignant metastases, lymphosarcomas or leukemic involvement can mimic IBC, thus delaying appropriate diagnosis and treatment [37]. IBC can be mistaken for infections and treated with antibiotics initially and only diagnosed as cancer after the antibiotics fail to reduce the symptoms. Accurate and timely diagnosis of IBC is critical due to the rapid progression of the disease.

In December 2009, an international panel of IBC experts defined guidelines based on consensus to facilitate the clinical diagnosis of IBC and to standardize the management of IBC. They specified the minimum criteria for the diagnosis of IBC to include a history of rapid onset of breast erythema, edema, and/or peau d'orange, and/or warm breast, with or without an underlying palpable mass, history of flattening, crusting, or retraction of the nipple. Furthermore, patients may have a history of being diagnosed with mastitis and not responding to at least one week of antibiotics and a duration of

history of no more than six months. Clinical examination should reveal erythema occupying at least one third of breast, and may involve an underlying palpable mass with or without palpable locoregional lymph node involvement and with or without nipple abnormalities. Pathological confirmation of invasive carcinoma from a core biopsy of the breast is required for diagnosis and it is recommended that an adequate skin punch biopsy be obtained to possibly document dermal lymphovascular tumor emboli involvement [38]. It has also been suggested to use characteristics from the medical history (rapid onset of symptoms, younger age, negative for bacterial infection), physical exam (nipple retraction, lymphadenopathy common) and mammographic findings in addition to the physical appearance and biopsy results for IBC diagnosis [35].

Debate over the relevance of dermal lymphatic invasion (DLI) in the diagnosis of IBC has hindered the use of a standardized diagnostic definition of IBC. Some experts prefer a pathologic definition of IBC inferring that DLI is required for IBC diagnosis [39, 40]. There is also a suggestion that pathologic confirmation of DLI could represent extent of disease, with earlier cases having less DLI [41]. Taylor and Meltzer considered IBC a clinical entity with dermal lymphatics providing pathological proof confirming but not denying diagnosis [42]. It is generally accepted that despite dermal lymphatic invasion being evident in as many as 50-75% of cases, it is not required for IBC diagnosis [43-45].

IBC may also be diagnosed when clinical symptoms are entirely lacking. This is termed Occult IBC and is characterized by the presence of tumor emboli in the dermal lymphatics with no clinical evidence of inflammation [40]. Occult IBC is extremely rare, estimated to comprise only 5% of all cases of IBC [8]. One retrospective study found

that patients with occult IBC showed a clearly different pattern of biological behavior as compared to IBC diagnosed clinically [46].

The most widely referenced case definition of IBC is that of the American Joint Cancer Committee (AJCC), which describes IBC as "a clinicopathologic entity characterized by diffuse erythema and edema (peau d'orange) of the breast, often without an underlying mass involving the majority of the breast" [47]. Accordingly, diagnosis of IBC can be made based on clinical signs and does not require pathologic evidence of dermal lymphatic invasion, though pathologic confirmation of breast cancer is required to distinguish IBC from benign disease [48]. IBC is classified as T4d breast carcinoma stage IIIb, IIIc, or even IV, depending on nodal status and evidence of distant metastasis according to the AJCC tumor-node-metastasis (TNM) coding [47]. Patients with locally advanced disease are designated as stage IIIb/c and those with metastatic disease are designated as stage IV.

The French tumor staging classification system for IBC is known as Pousee Evolutive (PEV) or rapidly progressing breast cancer in which the most advanced form, PEV 3, is defined as "a designation given to patients with inflammation covering more than half the breast surface" [49]. This definition is compatible with the AJCC case definition that has been used since the 1990's. PEV differs from TNM staging system in that it includes tumor growth characteristics and signs of inflammation.

The identification of IBC in the U.S. Surveillance, Epidemiology and End Results (SEER) registry data historically has been by the pathological codes (ICD-O-2 code for IBC -85303) specifically reserved for IBC with invasion of dermal lymphatic ducts. Reliance on tumor emboli for diagnosis may lead to underestimation of IBC incidence

when utilizing cancer registries [11]. It is likely that IBC cases without dermal lymphatic invasion comprise a considerable proportion of all IBC cases. Of the IBC cases diagnosed in the SEER program for 1975-1981, 92.6% of these cases did not have dermal lymphatic invasion [7].

Further, IBC cases may be identified in SEER registry using the Extent of Disease variable (EOD), which records a combined clinical and pathologic assessment of disease abstracted from the pathology report [33]. Since 1975, there have been four revisions to EOD coding procedures affecting IBC coding [50]. The most recent revision was in 1988 and it entailed no longer distinguishing between subtypes of IBC with and without dermal lymphatic invasion. Therefore, dermal lymphatic invasion has not been documented since 1988 and thus analyses by subtype of IBC are impossible since this rule change took effect. Since 1988, breast cancer cases have been assigned an EOD code 70 if their pathology reports described "diffuse dermal lymphatic permeation or infiltration" or "inflammatory carcinoma" whether or not IBC (SEER morphology 85303) was reported as final pathologic diagnosis. Between 1988 and 1992, it has been estimated that IBC was under-ascertained in the SEER registries by as much as 44% (322 IBC cases identifiable by EOD code only vs. 722 IBC cases identified by either ICD-O-2 85303 criteria or EOD) [33].

In 2003, the National Cancer Institute SEER program implemented a Multiple Primary and Histology (MP/H) task force to create rules to standardize the collection of multiple primary and histology information by tumor registries. As a result of this task force, the MP/H Coding Rules were created in 2007. Included is a rule that states that the International Classification for Oncology (ICD-O) histology code 8530 for IBC should

only be used "when the final diagnosis of the pathology report specifically states inflammatory carcinoma". Because IBC is typically clinically diagnosed rather than pathologically, most cases diagnosed on or after January 1, 2007 will not be identifiable using this histology code [51].

A study of prognostic factors in IBC found no prognostic value for the diagnostic selection group (clinical or pathologic definition) suggesting that either definition is justified to diagnose IBC [52]. However, in a meta-analysis, Kim et al found that the main cause of differences in treatment outcomes across studies was the variable criteria used to identify IBC [53]. SEER data for patients who received chemotherapy plus surgery and radiation therapy revealed that those with both clinical and pathologic diagnosis of IBC had a 3-year survival rate of 34% compared with 60% rate for patients with only clinical features of IBC and 52% for those with only pathologic diagnosis [43]. Thus, subtypes of IBC may exist with different prognosis depending on presence or absence of certain characteristics.

It has been noted that IBC may not be documented in cancer registries in developing countries, despite clinical characteristics of IBC being evident in the medical records. Further, information on tumor emboli involvement is often lacking in international registries and medical records. To address this issue, a multi-disciplinary group of physicians in Egypt and the United States, who were experienced in the diagnosis and management of IBC, collaboratively developed an 84-item checklist of symptoms, signs, and clinical characteristic suggestive of IBC to facilitate and standardize abstraction of information from medical records [54]. According to these criteria, IBC cases were identified using the simplified clinical definition of erythema,

edema, and peau d'orange as the three main clinical features of IBC. Subsequently, breast cancer cases seen at the Gharbiah Cancer Registry in Tanta, Egypt were grouped as follows: most-likely IBC exhibited all three features, possible IBC cases had any two of the three symptoms or had peau d'orange only, and non-IBC cases had edema only, erythema only, or had none of these three clinical features. Thus, IBC status was based on clinical criteria for diagnosis (erythema, edema, and peau d'orange). The checklist can be applied to all cases that have at least one of the three defining features of IBC and may be used to shed light on possible under-ascertainment of cases in cancer registries.

As diagnosis of IBC has changed over time and place, these differences must be considered when comparing IBC studies from distinct regions of the world and across different time periods. Comparing incidence of IBC between countries is severely limited due to the lack of a standardized case definition and uniform diagnostic criteria. Relying on a clinical diagnosis of IBC can lead to a wide variability in reporting and presents serious challenges for researchers when comparing studies of IBC and when assessing the accuracy of statistical data on the incidence of IBC [8].

Keeping these limitations in mind, the reported incidence of IBC varies greatly by region. It is been estimated that between 1% and 6% of all patients with breast cancer in the United States have IBC [7, 34,42]. Using clinical codes (EOD-E) in SEER indicates that IBC represents 2.5% of all incident breast cancer cases [8]. SEER data from 2005 shows 1.49% IBC as percentage of total breast cases in Connecticut while in rural Georgia, this percentage increases to 2.75% of total breast cases [6]. In Tunisia, it has been reported that up to 55% of breast cancer cases have IBC [9]. However, using a more uniform classification criteria, the incidence of IBC was subsequently estimated to

be 5-7% of newly diagnosed cases of breast cancer in Tunisia [10]. A population-based study confirmed that 11% of all breast cancers in Egypt are IBC, which is unequivocally higher than in the U.S. and most western countries where data are available [11]. Understanding the apparent geographic variability in the incidence of IBC is critical to our understanding of the etiology of this aggressive disease.

Risk Factors for inflammatory breast cancer

Despite a purported recent increase in incidence and the grim survival rates associated with IBC diagnosis, mechanisms underlying the etiology of this disease remain elusive. Based on the limited epidemiologic research on IBC, risk factors for the disease appear to be different from known risk factors for non-inflammatory breast cancer. Established risk factors for breast cancer include a long menstrual history (early menarche and late menopause), never having children, late age at first birth, small number of children and nulliparity, little or no breastfeeding, being overweight or obese after menopause, use of postmenopausal hormone therapy, physical inactivity, and consumption of one or more alcoholic beverages per day [55-62].

A recent population-based study found that younger age at onset, higher incidence in Blacks compared to Whites, pre-menopausal obesity and younger age at 1st birth may be risk factors for IBC in the U.S. and this study also emphasized the importance of investigating pre- and post-menopausal women separately [41]. In another study, IBC patients were found to be younger at menarche than non-inflammatory breast cancer

cases and non-breast cancer patients [63]. It has also been demonstrated that IBC patients were younger at the time of first live birth as compared to non-inflammatory breast cancer and non breast cancer patients [9, 33, 63, 64]. These study findings are intriguing because younger age at first birth has been shown to be protective against developing breast cancer. It is also suggested that younger age at first birth may be a risk factor for aggressive breast cancer in general. One study demonstrated a 3.2 fold increased odds (95% CI=1.2-8.49) of having high-grade breast cancer among women who had their first child before age 20 years [65]. Using the PEV classification system, pregnancy was associated with an incidence of 79% of rapidly progressing breast cancer, compared to 57% for non-rapidly progressing breast cancer (p=.01) and this was confirmed in subsequent studies [10, 66-68]. However, pregnancy and lactation have not been found to be predisposing factors to the development of IBC in the United States [34,42,69, 70].

Egyptian data revealed that premenopausal IBC patients had lower parity (p=.018) than non-inflammatory breast cancer patients, while the number of children was not significantly different between IBC and non-IBC postmenopausal patients (p=.243) [71]. The relationship between parity and IBC in a study in France and Tunisia was not significant but prolonged breastfeeding and younger age at menarche was associated with an increased risk of IBC [72]. Among 49 IBC cases in France, mostly of Algerian or Tunisian descent, duration of breast feeding exceeding 24 months (OR=6.7, p=.001), educational level less than 5 years (OR=4.5, p=.005) and body mass index greater than 30 (OR=4.2, p=.03) were all associated with diagnosis of IBC [73]. Obesity was shown to be a risk factor for premenopausal IBC but not for premenopausal non-IBC in one study

[41], while another study demonstrated that IBC patients had significantly higher BMI than both non-IBC patients and non-breast cancer patients irrespective of menopausal status [63].

Socioeconomics may play an important role in IBC risk, which is evident in the rural predominance of the disease in Tunisia and the comparison of IBC in North African migrants to France compared with French women living in the same region [73]. Rural residence and low SES as risk factors may suggest delay in diagnosis associated with increased clinical manifestation of IBC. In one study, approximately half of the cases with PEV positive breast cancer were living in rural areas, compared with only 30% of non-PEV positive cases [9]. This rural predominance was also found in another study in Tunisia where living in rural region was strongly associated with IBC (T4d) compared with non-IBC locally advanced breast cancer (LABC) patients (T4b) [10]. In a recent report of IBC in Tunisia, investigators reported a steady decline in IBC cases appearing in parallel with improved socioeconomic conditions in Tunisia [64].

Summary of background research

Examining the global occurrence of breast cancer is critical to understanding its etiology. International comparative analyses of breast cancer may help us recognize modifiable risk factors for this disease. Identifying risk factors for IBC can lead to targeted prevention efforts to prevent premature deaths and morbidity from this disease. Further, understanding IBC occurrence among the Arab American population is crucial for generating hypotheses about risk factors for this disease. Finally, IBC diagnosis is based on clinical and pathological characteristics and these criteria have changed over

time and place. These inconsistencies make international comparisons difficult. Investigating differences in IBC case ascertainment between distinct diagnostic criteria will be imperative in developing an ideal system for identification of cases to be utilized in studying the etiology of IBC globally.

1.3: Specific Aims and Hypotheses

Specific Aim 1

To examine trends in breast cancer incidence by age, stage, and hormone receptor status in Egypt from 1999-2008. Further, we evaluated the effect of possible changes in the population structure in order to make projections for breast cancer occurrence for the years 2009-2015.

Hypothesis: There will be an increasing trend in breast cancer incidence rates in Egypt from 1999-2008, and future breast cancer caseloads will increase particularly among the older age groups, due to the aging of the population. Further, we expect an increasing trend in localized breast cancer incidence due to recent early detection efforts and among estrogen receptor (ER) positive tumors due to the Westernization of the population.

Specific Aim 2

To describe the proportion of IBC out of all breast cancers among Arab Americans from Detroit, New Jersey and California SEER registries.

Hypothesis: There will be a higher proportion of IBC out of all breast cancers in Arab Americans as compared to non-Arab whites in Detroit, New Jersey and California.

Specific Aim 3

To ascertain the number of IBC cases at a single institution in Detroit, Michigan for a 2-year period (2007-2008) using clinical diagnostic criteria, which has been utilized in the Tanta, Egypt registry [1]. We will then compare the identified IBC cases to those recorded in SEER using the pathological code and the standard SEER IBC definition for this time period.

Hypothesis: The St Jean clinical criteria will identify more probable cases of IBC as compared to either the pathological or the standard SEER codes in the Detroit SEER registry for this time period.

Figure 1.1: Age-standardized breast cancer incidence and mortality rates per 100,000 by country

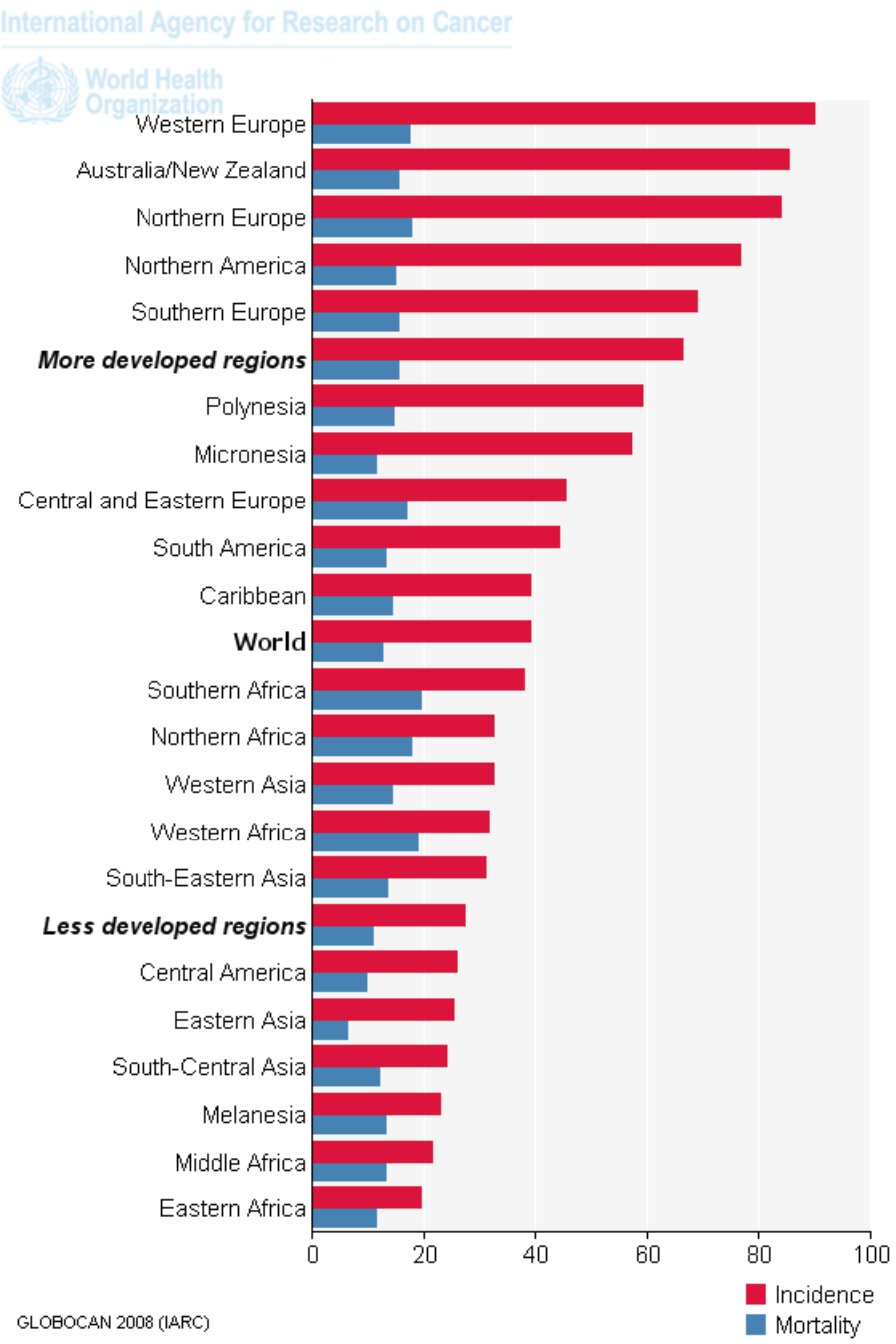

Image taken from: http://globocan.iarc.fr/

Figure 1.2: Dermal lymphatic invasion in inflammatory breast cancer (IBC)

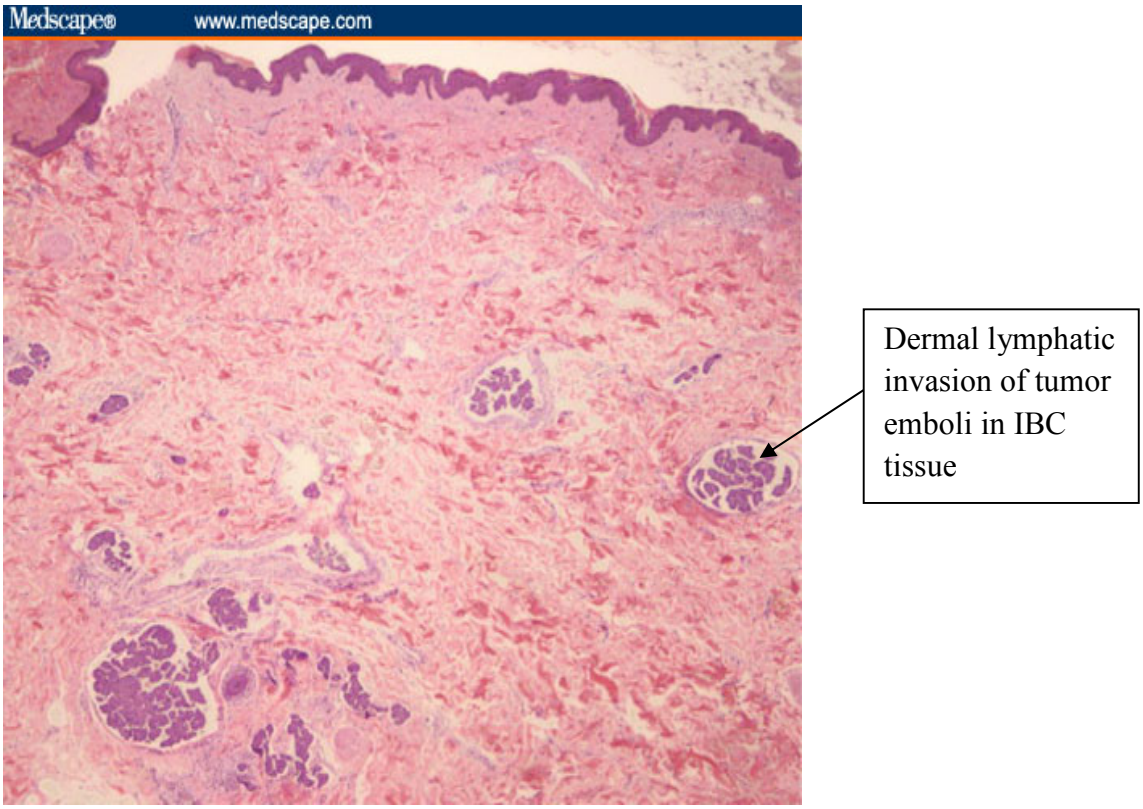

Image taken from: http://www.medscape.org/viewarticle/573516_3

Figure 1.3: Clinical characteristics of inflammatory breast cancer (IBC)

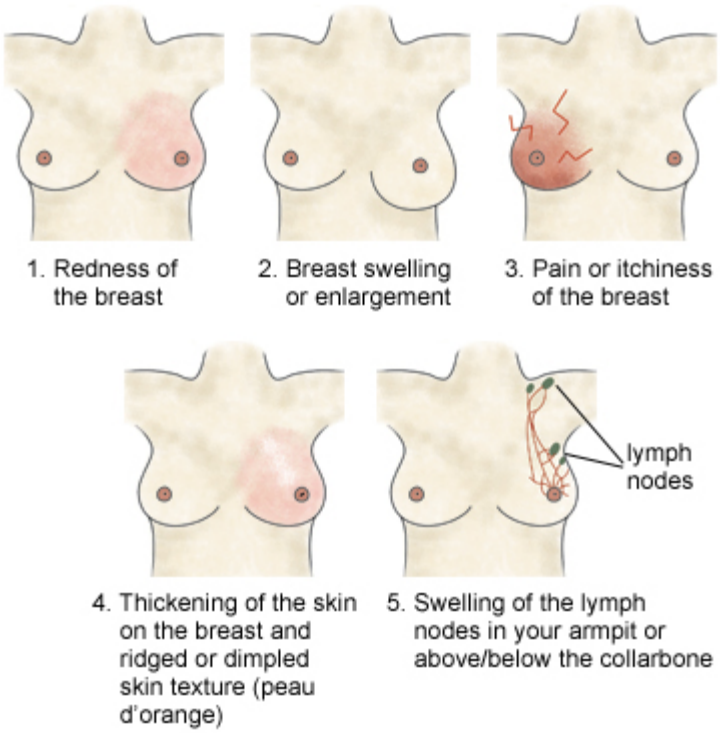

Image taken from: http://www.dana-farber.org/Health-Library/Symptoms-of-Inflammatory-Breast-Cancer.aspx

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Chapter 2

Trends in Breast Cancer Incidence Rates by Age, Stage, and Hormonal Status in Gharbiah, Egypt over 10 years (1999-2008)

2.1: Abstract

Breast cancer incidence is increasing in developing countries including Egypt. The Gharbiah Cancer Registry, the only population-based registry in Egypt, has been an effective resource for determining cancer incidence in Egypt since 1999. With the increasing cancer rates in developing countries, predicting cancer incidence is of critical value for planning cancer management and control policies. Therefore, this study was undertaken to evaluate trends in breast cancer incidence in Egypt from 1999-2008 and to make projections for breast cancer occurrence for the years 2009-2015.

We utilized joinpoint regression and average annual percent change (AAPC) measures with 95% confidence intervals (CI) to describe the trends in breast cancer incidence rates from the Gharbiah Cancer Registry by age, stage and hormonal status. We multiplied the most recent age-specific breast cancer incidence rates from 2008 by projected population

estimates from a linear regression model to estimate expected future breast cancer caseloads from 2009-2015 by age group, stage at diagnosis, and hormone receptor status and characterized trends using AAPC measures in joinpoint regression.

From 1999-2008, the AAPC in breast cancer incidence rates in Gharbiah significantly increased among women 50 years and older, and among localized tumors (AAPC=5.5%, 95% CI, 3.1% to 8.0%), and ER negative tumors (AAPC=7.6%, 95% CI=2.6%, 12.9%). Our results predict a significant increase in breast cancer caseloads from 2009-2015 among women ages 30-39 (AAPC=1.0%, 95% CI, 0.9% to 1.1%) and among women 40-49 years (AAPC=1.8%, 95% CI, 1.0% to 2.6%). The greatest expected increase in ER negative tumors from 2009-2015 is among women 70 years and older (AAPC=5.0%, 95% CI=1.7% to 8.3%).

These results have important implications for allocating limited resources, managing treatment needs, and exploring the consequences of prior interventions and/or changing risk factors in Egypt and other developing countries at the same stages of demographic and health transitions.

2.2: Background

Breast cancer rates are increasing in developing countries including Egypt, and are largely attributed to aging of the population, delay in time of first pregnancy, decrease in number of children and in breastfeeding, increase in use of external hormones, and a move toward high-calorie Western diets [1-4]. Although breast cancer incidence rates in

Egypt are substantially lower than the rates in the United States and other developed countries [5-7], breast cancer is the most common cancer among women in Egypt [8]. The average age at diagnosis of breast cancer in Egypt is approximately a decade earlier than the age of diagnosis in Western countries [9]. This is likely due to the differences in the population structures between the countries, with a larger proportion of the Egyptian population in the younger age groups than in Western countries [10].

The aging of the population in Egypt is largely attributed to increasing life expectancy, control of infectious diseases, and declining fertility rates [11]. The United Nations population projections for Egypt included in a 1997 report predict that the total fertility rate will decrease to two children per woman by 2020-2025 [12], and that the overall population will increase by approximately 84.4% over the current population figure by 2065 [13]. By the year 2020, 14.3 million Egyptian women are expected to be in the prime childbearing ages of 20-40, compared with 9.2 million in 1999 [14]. Therefore, the increase in the number of women in their childbearing years will result in an overall population growth. Life expectancy in Egypt has also improved from 63.3 years among those born in 2000 to 72.66 years among those born in 2011 [15]. Therefore, it is expected that over the next several decades the proportion of older women will constitute a larger stratum of the population than currently observed, and older age is associated with higher breast cancer rates [16]. In summary, the current demographic trends favor the likelihood that breast cancer will become an even greater public health concern in Egypt in the future.

There is evidence to suggest that hormonal subtypes of cancer differ in developing and developed countries, with estrogen receptor (ER) positive tumors being

more common in developed countries [17]. Hormonal receptor subtypes of breast cancer are important to consider due to their differential response to therapy, with better prognosis overall for ER positive tumors [18,19]. Little information is available on recent trends of breast cancer by hormonal subtype in Egypt, though our previous study demonstrated higher incidence of ER positive tumors in urban areas as compared to rural areas in Egypt [20]. Information on trends in hormonal receptor status of breast cancers would be valuable for cancer planning efforts in Egypt, a setting with limited treatment resources. Moreover, the majority of breast cancers in Egypt are detected at advanced stage [21], although recent efforts toward increasing awareness and breast self exam have been made to downstage breast cancer, despite the lack of widespread screening. Trends in the stage at diagnosis of breast cancer in the Gharbiah registry have not been reported, and this information is critical for evaluation of the downstaging efforts.

Annual breast cancer incidence rates have been reported for the only population-based registry of Gharbiah, Egypt from 1999-2006 [20-21]. However, no reports have been published on the breast cancer trend for the data that are available in Egypt over the past 10 years. Detailed information on trends of breast cancer by stage and hormonal receptor status may promote the reduction of disparities in the presentation of disease by focusing limited resources on the susceptible populations, and can aid in our overall understanding of the etiology of breast cancer in a setting that differs in regard to its risk factor profile as compared to many developed countries. Therefore, the specific aim of this study was to examine trends in breast cancer incidence by age, stage, and hormone receptor status in the Gharbiah registry from 1999-2008. Further, we evaluated the effect

of possible changes in the population structure in order to make projections for breast cancer occurrence for the years 2009-2015.

2.3: Methods

Gharbiah population-based cancer registry

The Gharbiah population-based cancer registry is located in Tanta, the capital city of the Gharbiah province. The population of Gharbiah is about 3.4 million and the registry was founded in 1998 as part of the Middle East Cancer Consortium (MECC) [1]. Data on cancer cases are actively collected from various sources throughout the province of Gharbiah. Strict quality control checks are adhered to and data are entered using the International Agency for Research on Cancer (IARC) software CanReg4. Registrars are routinely trained in data extraction and entry methods and are periodically monitored by faculty of Emory School of Public Health, IARC, and MECC [1]. Coding of cancer is based on the International Classification of Diseases for Oncology 10th edition [22].

Study Population

A total of 7,049 cases of female breast cancer diagnoses were entered in the Gharbiah population-based cancer registry from 1999-2008. We excluded 52 cases with tumor behavior coded as uncertain or in situ, leaving 6,997 invasive cases for our study sample. For each case, the following information from routinely-collected registry data was obtained for this analysis: age at diagnosis, ER status, progesterone receptor (PR) status, summary stage at diagnosis, laterality of tumor and basis for diagnosis. ER and PR status were determined by immunohistochemical results from the centers providing

cases to the registry. We restricted our analysis on ER and PR status to the years 2001-2008, when this information was more routinely collected in the registry. The Surveillance, Epidemiology and End Results (SEER) Summary Staging system was used to code stage at diagnosis [23]. Localized tumors were defined as those confined entirely to the organ of origin; regional tumors were those that extended into surrounding organs, tissues, or regional lymph nodes; and distant tumors were those that had spread to distant organs or lymph nodes.

Statistical Analysis

Breast cancer incidence data from 1999-2008 were obtained from the Gharbiah Cancer registry. The average annual percent change (AAPC) in breast cancer rates was calculated using joinpoint regression for the age-specific incidence rates of breast cancer overall and by stage and hormonal receptor status. The AAPC over the fixed interval of 1999-2008 is a weighted average of the slope coefficients of the underlying joinpoint regression line with the weights equal to the length of each segment over the interval [24].

Census data for female population in Gharbiah were obtained from the 1996 and 2006 Central Agency for Public Mobilization and Statistics (CAPMAS) census [25], and constant growth of the population was assumed to predict population estimates for the non-censal years using a linear regression model. We combined women under the age of thirty years into a single category due to the relative rarity of breast cancer in this age group. The projected population numbers were multiplied by the most recent age-specific breast cancer incidence rates available from 2008 to estimate projected breast

cancer caseloads by age group in Gharbiah, Egypt from 2009 through 2015 accounting for population changes. Joinpoint regression models were fit to the predicted caseloads and AAPCs were utilized to describe trends in the projected future breast cancer cases. Data analysis was performed using Joinpoint Regression program [20] and SAS version 9.0 (SAS Institute Inc, Cary, NC); $P \leq .05$ was used to determine statistical significance. The study was approved by the University of Michigan Institutional Review Board and the Gharbiah Cancer Center Ethics Committee.

2.4: Results

The majority of breast cancer cases during the study period were diagnosed among women aged 40-49 years (31.8%) and among women aged 50-59 years (29.8%) (Table 1). Most breast cancers were ER positive (36.9%) and PR positive (25.7%) (Table 1). Nearly all of the breast cancers were diagnosed microscopically (histology of primary 78.9% and FNAC 17.5%) and 49.7% were diagnosed at a regional stage of disease (Table 1). Based on limited hormonal receptor data, the percentage of ER positive tumors decreased from 34.7% in 2001 to 27.2% in 2008 and the percentage of ER negative tumors increased from 11.0% in 2001 to 15.9% in 2008 (Table 1). The percentage of localized breast tumors increased over the study period, from 14.8% of tumors in 1999 to 21.4% of breast tumors in 2008 (Table 1).

Trends by age at diagnosis

Women aged 50-59 years had the highest overall breast cancer incidence rates through the years 1999-2008 (Figure 1). The overall breast cancer incidence rates increased in Gharbiah, Egypt from 1999-2008 by an AAPC of 2.3% (95% CI =1.5%, 3.0%) (Table

2). A significant increase in breast cancer incidence was evident among women aged 50 years and older, and the highest AAPC of 5.1% (95% CI = 1.2%, 9.2%) was noted among women aged 70 years and older (Table 2). The highest rate of population growth from 1999-2008 was evident among women aged 50-59 years (Figure 2). Using 1999-2008 rates to predict 2009-2015 rates, we expect a significant increase in the breast cancer caseloads from 2009-2015 among women ages 30-39 years (AAPC=1.0%, 95% CI 0.9%, 1.12%) and among women aged 40-49 years (AAPC=1.8%, 95% CI=1.0%, 2.6%) (Table 3).

Trends by stage at diagnosis

The AAPC in the overall breast cancer incidence rates increased for localized tumors by 5.5% (95% CI=3.1%, 8.0%), and for regional tumors by 2.6% (95% CI=1.0%, 4.3%), and there was a significant decrease in distant tumors among women aged 30-49 years (Table 4). The greatest increase in the incidence of localized tumors was evident among women aged 60-69 years with an AAPC of 9.4% (95% CI=3.5%, 15.7%) (Table 4). The incidence of breast tumors diagnosed at a distant stage of disease decreased among women aged 30-39 years (AAPC=-11.3%, 95% CI=-19.6%, -2.1%) and among women aged 40-49 years (AAPC=-5.4%, 95% CI=-10.2%, -0.2%) (Table 4) . Overall breast cancer caseloads are expected to increase annually from 2009-2015 among localized tumors by 1.3% (95% CI=1.2%, 1.4%), among regional tumors by 1.3% (95% CI=1.3%, 1.4%) and among distant tumors by 1.4% (95% CI=1.2%, 1.7%). (Table 5) The greatest expected increase in breast cancer caseloads are among women aged 50-59 years for

localized (AAPC=2.9%, 95%CI=2.5%, 3.2%), regional (AAPC=2.7%, 95% CI=2.6%, 2.8%) and distant tumors (AAPC=2.4%, 95%CI=1.7%, 3.2%) (Table 5).

Trends by hormonal receptor status

Overall, there was a significant increase in the incidence of ER negative tumors (AAPC=7.6%, 95% CI=2.6%, 12.9%), PR positive tumors (AAPC=10.7%, 95% CI=0.7%, 21.7%) and PR negative tumors (AAPC=4.5%, 95% CI=1.3%, 7.8%) based on the limited available data on hormonal receptor status (Table 6). The greatest increase in the incidence of ER negative tumors from 2001-2008 was evident among women aged 50-59 years (AAPC=11.2%, 95%CI=2.5%, 20.6%) (Table 6). We can expect an AAPC of 5.0% (95% CI=1.7%, 8.3%) among ER negative tumor caseloads among women ages 70+ (Table 7).

2.5: Discussion

This study demonstrated a considerable increase in breast cancer incidence rates in Gharbiah, Egypt from 1999-2008, particularly among women 50 years and older. While breast cancer incidence rates are increasing among older women, we found that the greatest expected increase in breast cancer caseloads for 2009-2015 is among women aged 30-49 years due to population changes. Further, our study noted a general decline in the incidence of distant tumors in Gharbiah, Egypt from 1999-2008, and a significant increase in the incidence of ER negative tumors, with the greatest increase in ER negative tumors from 2009-2015 expected among women aged 70 years and older.

Established risk factors for breast cancer include a long menstrual history, never having children, late age at first birth, small number of children and nulliparity, little or

no breastfeeding, being overweight or obese after menopause, use of postmenopausal hormone therapy, physical inactivity, and consumption of one or more alcoholic beverages per day [26-34]. Trends in reproductive factors and obesity associated with breast cancer favor the increase in breast cancer incidence in Egypt. For example, the fertility rate in Egypt is declining [7] and obesity is on the rise [35]. The overall obesity rate in Egypt in 2006 was 30.3% [15] and an increasing prevalence of obesity among Egyptian women has been reported [36]. Furthermore, in Egypt urban residence is clearly related to obesity risk [37-39] and the rate of urbanization from 2010-15 is estimated at 2.1% annual rate of change [15]. Thus, the increasing urbanization of the population in Egypt could have implications on breast cancer trends through its effect on obesity. Moreover, reproductive risk factors for breast cancer may be influenced by obesity trends. One study found that Egyptian girls who were overweight or obese were more likely to undergo menarche at an earlier age as compared to those with a normal BMI [40]. This means that obesity can influence the length of time that women's bodies are exposed to endogenous hormones, thus increasing one's risk for breast cancer. Information on the prevalence of post-menopausal hormone therapy (HRT) in Egypt is difficult to obtain; however, one study conducted among menopausal women in Alexandria, Egypt found that 91% of women had never heard of HRT [41]. Therefore, we do not suspect that use of HRT has played a large role in the increase in incidence of breast cancer among Egyptian women.

We found little information on physical activity trends in Egypt, although one report suggested that a large proportion of the population in Egypt is quite sedentary, particularly in urban areas [36]. Alcohol use is unlikely to account for the increase in

breast cancer incidence in Egypt, where the majority of the population adheres to the Muslim religion, which prohibits use of alcohol.

Promotion of breast cancer by environmental agents is suspected to occur because many of these chemicals behave in vivo and in vitro much like estrogen [42]. There has been some concern about the role of chemicals that can mimic estrogen, termed xenoestrogens, including pesticides containing organochlorines, such as dichlorodiphenyltrichloroethane (DDT) in cancer. The level of pesticides like DDT is higher in the developing world than the developed world and DDT is found to be positively associated with breast cancer risk [43]. Further, evidence of an association between the incidence of postmenopausal breast cancer and exposure to ambient concentrations of NO2 from air pollution has been reported [44]. Air pollution in Egypt is a significant health concern resulting from the increase of automobile exhaust, fuel and burning operations in cities [45]. In summary, changes in the prevalence of established risk factors for breast cancer in Egypt may partially explain the increased incidence reported in this study, although future research should investigate other contributing factors.

The latent period between exposure to risk factors and the manifestation of disease may account to some extent for the observed trend of a statistically significant increase in breast cancer incidence only among women 50 years and older. For example, the effects of the Westernization of the Egyptian population may take several decades to develop into a detectable breast cancer increase. Therefore, the ill effects of the relatively recent adoption of a Western lifestyle may not have yet emerged in the younger age groups. Furthermore, there may be something inherent in the breast tissue of older

women, which makes them more susceptible to the changing risk factor profile for breast cancer. These findings may also be attributed to the larger number of cases in the older women, providing greater power to demonstrate a statistically significant measure.

Our finding of the greatest expected increase in breast cancer caseloads among younger women aged 30-49 largely reflects the increase in the population size among this age group; these results do not necessarily imply that screening efforts should target this age group. The incidence among younger age groups is very low and many women would have to be screened to find the cases. Therefore, in our opinion, awareness among younger women and education on breast self exam may be the best approach to accomplish early detection among the younger age groups.

Our finding of a general decline in incidence of distant tumors is encouraging given the emphasis on early detection and the screening efforts that have been occurring in Egypt over the study period. However, because of the overall population growth in Egypt, we can still expect a significant increase in breast tumors of all stages from 2009-2015. Therefore, while downstaging efforts are likely to be effective in reducing the incidence of breast tumors diagnosed at an advanced stage, Egypt must still be prepared to cope with the increased burden of diagnosing and treating breast tumors at all stages of disease.

Most of the increase in breast cancer incidence in the United States has been due to an increase in ER positive breast cancer [46]. Reproductive factors that increase women's lifetime exposure to endogenous estrogens result in ER positive cancers, while smoking, radiation and genetic risks are thought to give rise to ER negative cancers [47-49]. Alcohol consumption and family history of breast cancer has been shown to be

associated with breast cancer regardless of ER status [50]. Thus, established risk factors for breast cancer associated with the Westernization of the population in Egypt would be more likely to explain an increase in ER positive tumors. However, this study demonstrated a significant increase in the incidence of ER negative tumors, with the greatest expected increase in ER negative tumors from 2009-2015 among women 70 years and older. Breast cancer cases with BRCA1 and BRCA2 gene mutations are more likely to be ER negative [51-58] and these mutations are responsible for a significant proportion of breast cancer in Egypt [59]; however, it is unlikely that the prevalence of this gene mutation increased significantly in the time period of our study to account for the overall incidence trends in ER negative tumors. Future research should focus on risk factors that may illuminate the increasing trends of ER negative tumors in Egypt, especially among older women. This information is critical to cancer treatment planning and may also provide insight into the etiology of the hormonal subtypes of breast cancer. Finally, while this study noted significant increases in both PR positive and PR negative tumors, the percent distribution of breast tumors by PR status remained relatively constant throughout the study years 1999-2008. Therefore, this increase largely reflects the increasing tendency to report PR status in the records throughout the study years.

This study does have several important limitations that need to be considered. Most importantly, the stage at diagnosis and hormonal receptor status information was missing for a large proportion of the breast cancer cases in our analysis. The persistence of unknown stage and hormonal receptor status throughout the study years is disconcerting. Stage at diagnosis and hormonal receptor status information are critical metrics for treatment planning and for evaluation of cancer control programs. We believe

that reporting of this information must be prioritized and that the specific challenges in reporting this information should be identified and ameliorated with urgency. Furthermore, we found statistically significant differences in the percentage of missing stage data across age groups and regions contributing cancer cases to the Gharbiah registry, with the greatest percent of missing stage data coming from the non-specialized hospitals and clinics, pathology labs as well as cases registered via death certificates only. Missing stage data was most notable among women ages 70+ (data not shown) and this may be due to the higher likelihood of diagnosis by fine needle aspirate (FNA) without tissue pathology available for staging among this age group. The incidence of breast cancer cases with unknown hormonal receptor status was previously shown to be similar from 1999-2006, and cases with unknown hormonal receptor status were similar to the overall breast cancer cases in the Gharbiah registry in regard to important baseline factors like age and stage at diagnosis [20]. However, we found that ER and PR information was more likely to be missing among women aged 70+ and among tumors diagnosed at a distant stage of disease (data not shown). Diagnosis by FNA among older women and those diagnosed at a distant stage of disease may explain this trend, as tissue would be unavailable for pathological staging or hormonal assays.

The missing stage and hormonal status information could have limited our ability to demonstrate a significant measure of trend and could produce bias in our estimates of the trends in breast cancer occurrence in Egypt. This issue of missing hormonal receptor status is not unique to the Gharbiah registry. For example, one study of SEER data documented that between 1992-2007, 17% of cases had missing ER data and that the likelihood of missing data increased with increasing age at diagnosis and increasing stage

of disease [60]. In summary, we must be extremely cautious in making inferences based on the observed trends in light of the fact that there was a significant amount of missing data for stage and hormonal receptor status that could have biased results.

A further limitation of this study is the fact that the breast cancer projections reported in this study assume stable screening practices, risk factor profiles and constant incidence rates from 2008. Future predictions are affected by population growth and by aging and changing risk factors, which may be difficult to predict. Thus, while the projections reported in this study are based on statistical models, they should be interpreted with some caution. The further from 2008 the predicted caseloads are, the more prone to error the estimates will be. Moreover, the population figures for the years between the census were determined using linear interpolation, which assumes constant growth over these years. The accuracy of the calculated incidence rates would be affected if the actual population figures differ from our predicted values. Additionally, registry-specific statistics are based on small numbers of cases per year observed in young women, with an inevitable high degree of variability. Finally, interpretation of the increased incidence of breast cancer is not straightforward because the possibility of increased detection and improved quality of data collection and classification are difficult to differentiate [61]. While advances in diagnostic technology may have had some effect on the apparent increasing incidence of breast cancer over the study period, screening is not widespread in Egypt. One study noted participation in a voluntary clinical breast exam screening program in Egypt of 10.2% with abnormal findings evident in 3.2% of cases [62]. Therefore it is unlikely that increased detection of breast cancer accounts for the observed increasing trends in breast cancer incidence in Egypt.

Strengths of this study include the use of a well-characterized and validated population-based registry data from a 10-year period. In addition, this study provides predictions for future trends, which are critical to cancer control and planning efforts in Egypt. Finally, this study provides important information on the progress of downstaging efforts in Egypt and also details trends in hormonal receptor status of tumors, which is critical for cancer treatment planning, especially in developing countries with limited treatment resources.

Cancer incidence is rising around the world due to population growth, aging, the impact of changes in behavioral risk factors, and reduced mortality from infectious diseases [63]. The developing world may be ill-prepared to deal with the consequences of cancer diagnosis both financially and socially. The lack of infrastructure and financial assets may lead to additional suffering associated with a cancer diagnosis, some of which could be avoided with increased resources. Therefore, breast cancer in Egypt is a growing public health concern and significant efforts should be directed to addressing the increasing burden of breast cancer in this part of the world.

In conclusion, this study demonstrated that the breast cancer burden in Egypt will likely increase given the current population trends. The observed breast cancer incidence trends are consistent with the aging and Westernization of the population in Egypt; however, the increase in ER negative tumors warrants future research into the potential risk factors accounting for this trend. Our results have important implications for allocating limited resources, managing treatment needs, and exploring the consequences of prior interventions and/or changing risk factors in Egypt and other developing countries at the same stages of demographic and health transitions.

Table 2.1: Characteristics of breast cancer cases (n=6,997) by year of diagnosis in Gharbiah, Egypt, 1999-2008

	Year of diagnosis											
Characteristic	1999 n (%)	2000 n (%)	2001 n (%)	2002 n (%)	2003 n (%)	2004 n (%)	2005 n (%)	2006 n (%)	2007 n (%)	2008 n (%)	Overall n (%)	p-value[a]
Age												
0-29	18 (2.9)	15 (2.5)	10 (1.6)	22 (3.5)	14 (2.0)	15 (2.1)	21 (2.9)	9 (1.2)	13 (1.7)	22 (2.6)	159 (2.3)	0.0051
30-39	103 (16.6)	107 (18.0)	110 (17.5)	104 (16.5)	115 (16.9)	103 (14.4)	100 (13.7)	101 (13.0)	88 (11.2)	113 (13.5)	1044 (14.9)	
40-49	215 (34.7)	180 (30.4)	214 (34.1)	195 (30.9)	223 (32.7)	216 (30.3)	229 (31.5)	263 (33.8)	235 (29.9)	253 (30.2)	2223 (31.8)	
50-59	164 (26.5)	177 (29.9)	172 (27.4)	178 (28.2)	198 (29.0)	218 (30.5)	209 (28.7)	244 (31.4)	255 (32.5)	271 (32.3)	2086 (29.8)	
60-69	94 (15.2)	76 (12.8)	77 (12.3)	91 (14.4)	101 (14.8)	109 (15.3)	117 (16.1)	110 (14.1)	129 (16.4)	122 (14.6)	1026 (14.7)	
70+	26 (4.2)	38 (6.4)	45 (7.2)	41 (6.5)	31 (4.6)	53 (7.4)	52 (7.1)	51 (6.6)	65 (8.3)	57 (6.8)	459 (6.6)	
Overall	620 (8.9)	593 (8.5)	628 (9.0)	631 (9.0)	682 (9.8)	714 (10.2)	728 (10.4)	778 (11.1)	785 (11.2)	838 (12.1)	6997 (100)	
ER[b]												
Positive	n/a	n/a	218 (34.7)	193 (30.6)	214 (31.4)	265 (37.1)	265 (36.4)	391 (50.3)	356 (45.4)	228 (27.2)	2130 (36.9)	<.0001
Negative	n/a	n/a	69 (11.0)	92 (14.6)	112 (16.4)	112 (15.7)	127 (17.4)	148 (19.0)	137 (17.5)	133 (15.9)	930 (16.1)	
Missing	n/a	n/a	341 (54.3)	346 (54.8)	356 (52.2)	337 (47.2)	336 (46.2)	239 (30.7)	292 (37.2)	477 (56.9)	2724 (47.1)	
PR[c]												
Positive	n/a	n/a	126 (20.1)	110 (17.4)	135 (19.8)	157 (22.0)	194 (26.6)	314 (40.3)	272 (34.6)	181 (21.6)	1489 (25.7)	<.0001
Negative	n/a	n/a	98 (15.6)	104 (16.5)	111 (16.3)	104 (14.6)	115 (15.8)	125 (16.1)	160 (20.4)	139 (16.6)	956 (16.5)	
Missing	n/a	n/a	404 (64.3)	417 (66.1)	436 (63.9)	453 (63.4)	419 (57.6)	339 (43.6)	353 (45.0)	518 (61.8)	3339 (57.7)	
Stage												
Localized	92 (14.8)	106 (17.9)	143 (22.8)	138 (21.9)	142 (20.8)	137 (19.2)	160 (22.0)	177 (22.8)	181 (23.1)	179 (21.4)	1455 (20.8)	<.0001
Regional	314 (50.6)	275 (46.4)	313 (49.8)	323 (51.2)	327 (47.9)	360 (50.4)	359 (49.3)	387 (49.7)	365 (46.5)	453 (54.1)	3476 (49.7)	
Distant	87 (14.0)	95 (16.0)	83 (13.2)	71 (11.3)	100 (14.7)	94 (13.2)	77 (10.6)	77 (9.9)	95 (12.1)	55 (6.6)	834 (11.9)	
Missing	127 (20.5)	117 (19.7)	89 (14.2)	99 (15.7)	113 (16.6)	123 (17.2)	132 (18.1)	137 (17.6)	144 (18.3)	151 (18.0)	1232 (17.6)	

Laterality												
Right	267 (43.1)	255 (43.0)	261 (41.6)	269 (42.6)	287 (42.1)	327 (43.0)	307 (42.2)	351 (45.1)	319 (40.6)	405 (48.3)	3048 (43.6)	<.0001
Left	284 (45.8)	273 (46.0)	324 (51.6)	332 (52.6)	344 (50.4)	340 (51.8)	370 (50.8)	373 (47.9)	398 (50.7)	399 (47.6)	3437 (49.1)	
Bilateral	5 (0.8)	3 (0.5)	6 (1.0)	5 (0.8)	9 (1.3)	5 (1.1)	8 (1.1)	5 (0.6)	2 (0.3)	5 (0.6)	53 (0.8)	
Missing	64 (10.3)	62 (10.5)	37 (5.9)	25 (4.0)	42 (6.2)	42 (6.0)	43 (5.9)	49 (6.3)	66 (8.4)	29 (3.5)	459 (6.6)	
Basis[d]												
Histology	398 (64.2)	469 (79.1)	468 (74.5)	518 (82.1)	553 (81.1)	571 (80.0)	592 (81.3)	652 (83.8)	626 (79.8)	673 (80.3)	5520 (78.9)	<.0001
FNAC[e]	168 (27.1)	83 (14.0)	142 (22.6)	99 (15.7)	105 (15.4)	118 (16.5)	113 (15.5)	107 (13.8)	138 (17.6)	150 (17.9)	1223 (17.5)	
Others[f]	54 (8.7)	40 (6.7)	18 (2.9)	14 (2.2)	23 (3.4)	24 (3.4)	23 (3.2)	19 (2.4)	21 (2.7)	15 (1.8)	251 (3.6)	
Missing	0 (0.0)	1(0.2)	0 (0.0)	0(0.0)	1(0.1)	1 (0.1)	0 (0.0)	0(0.0)	0(0.0)	0(0.0)	3 (0.0)	

[a]=p-value based on chi-square test
[b]=Estrogen receptor status
[c]=Progesterone receptor status
[d]= Basis for diagnosis
[e]=Fine needle aspiration cytology
[f]=Clinical only, ultrasound, x-ray, exploratory surgery or autopsy, specific biochemical or immunohistochemical test

Figure 2.1: Breast Cancer Incidence Rates/100,000 person-years by age group and year of diagnosis, 1999-2008

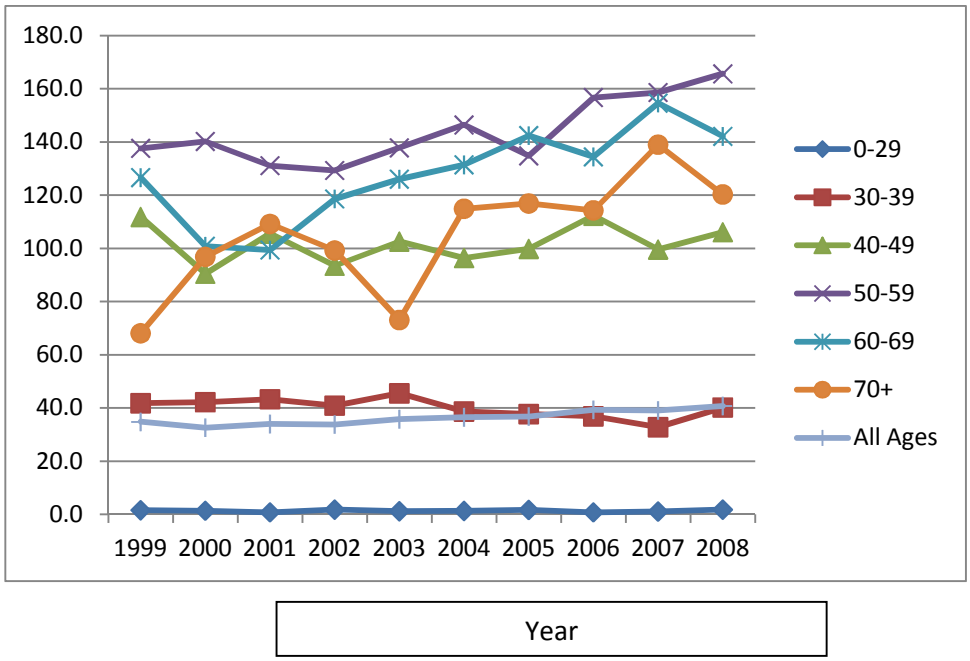

Table 2.2: Average Annual Percent Change (AAPC) in Breast Cancer Incidence Rates/100,000 person-years by age group, 1999-2008

Agegroup	Years	AAPC[a]	LCL[b]	UCL[c]
0-29	1999-2008	0.0%	-6.9%	7.5%
30-39	1999-2008	-1.9%	-3.7%	0.0%
40-49	1999-2008	0.3%	-1.6%	2.2%
50-59	1999-2008	**2.3%**	**0.8%**	**3.7%**
60-69	1999-2008	**3.6%**	**1.2%**	**6.0%**
70+	1999-2008	**5.1%**	**1.2%**	**9.2%**
Overall	1999-2008	**2.3%**	**1.5%**	**3.0%**

[a] Average Annual Percent Change
[b] Lower Confidence Limit (95% Confidence Interval)
[c] Upper Confidence Limit (95% Confidence Interval)

Figure 2.2: Average annual percent change (AAPC) with lower (LCL) and upper (UCL) confidence levels in population by age group from 1999-2008

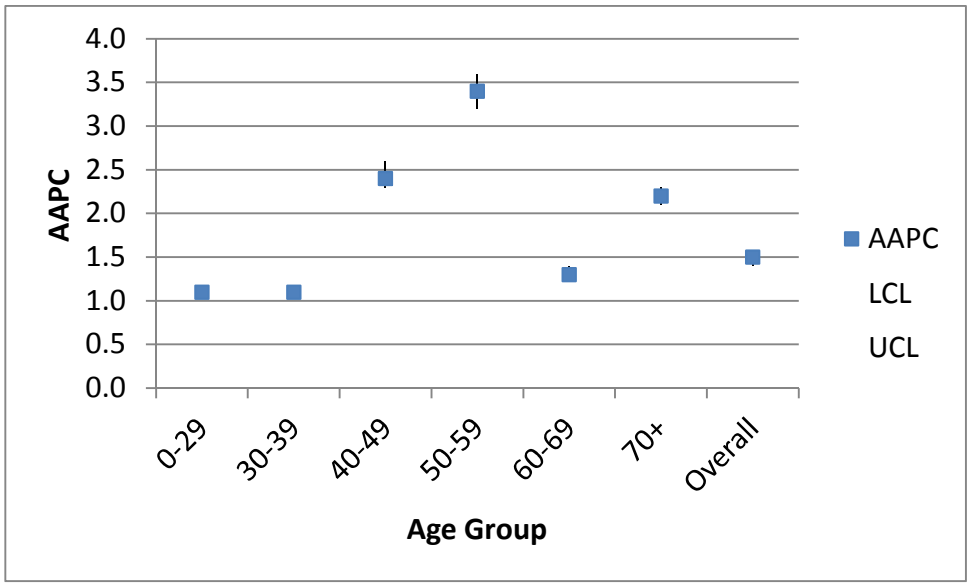

Table 2.3: Average Annual Percent Change (AAPC) in breast cancer caseloads by age group, predictions for years 2009-2015

Agegroup	Years	AAPC[a]	LCL[b]	UCL[c]
0-29	2009-2015	-0.2%	-4.7%	4.6%
30-39	2009-2015	**1.0%**	**0.9%**	**1.1%**
40-49	2009-2015	**1.8%**	**1.0%**	**2.6%**
50-59	2009-2015	1.8%	-0.7%	4.5%
60-69	2009-2015	0.5%	-1.5%	2.5%
70+	2009-2015	1.1%	-1.2%	3.4%
Overall	2009-2015	1.4%	-0.2%	3.1%

[a] Average Annual Percent Change
[b] Lower Confidence Limit (95% Confidence Interval)
[c] Upper Confidence Limit (95% Confidence Interval)

Table 2.4: Average Annual Percent Change (AAPC) in Breast Cancer Incidence Rates/100,000 person-years by summary stage & age group

Stage	Agegroup	Years	AAPC[a]	LCL[b]	UCL[c]
Localized	0-29	1999-2008	-2.7%	-16.2%	13%
	30-39	1999-2008	-1.3%	-6.4%	4.1%
	40-49	1999-2008	**5.8%**	**2.4%**	**9.3%**
	50-59	1999-2008	3.1%	-1.8%	8.3%
	60-69	1999-2008	**9.4%**	**3.5%**	**15.7%**
	70+	1999-2008	18.2%	-1.7%	42.0%
	Overall	1999-2008	**5.5%**	**3.1%**	**8.0%**
Regional	0-29	1999-2008	-0.5%	-11.1%	11.4%
	30-39	1999-2008	-0.9%	-3.9%	2.3%
	40-49	1999-2008	-0.7%	-3.4%	2.0%
	50-59	1999-2008	**3.8%**	**1.2%**	**6.4%**
	60-69	1999-2008	**4.7%**	**1.8%**	**7.7%**
	70+	1999-2008	6.6%	-2.5%	16.6%
	Overall	1999-2008	**2.6%**	**1.0%**	**4.3%**
Distant	0-29	1999-2008	-45.7%	-76.2%	23.8%
	30-39	1999-2008	**-11.3%**	**-19.6%**	**-2.1%**
	40-49	1999-2008	**-5.4%**	**-10.2%**	**-0.2%**
	50-59	1999-2008	-2.2%	-9.4%	5.5%
	60-69	1999-2008	-4.9%	-11.4%	2.1%
	70+	1999-2008	3.8%	-8.6%	18.0%
	Overall	1999-2008	-4.0%	-8.2%	0.4%

[a] Average Annual Percent Change
[b] Lower Confidence Limit (95% Confidence Interval)
[c] Upper Confidence Limit (95% Confidence Interval)

Table 2.5: Average Annual Percent Change (AAPC) in breast cancer caseloads by summary stage and age group, predictions for years 2009-2015

Stage	Agegroup	Years	AAPC[a]	LCL[b]	UCL[c]
Localized	0-29	2009-2015	0.0%	0.0%	0.0%
	30-39	2009-2015	**0.9%**	**0.1%**	**1.7%**
	40-49	2009-2015	**2.1%**	**1.9%**	**2.4%**
	50-59	2009-2015	**2.9%**	**2.5%**	**3.2%**
	60-69	2009-2015	**1.0%**	**0.6%**	**1.4%**
	70+	2009-2015	**2.2%**	**0.9%**	**3.5%**
	Overall	2009-2015	**1.3%**	**1.2%**	**1.4%**
Regional	0-29	2009-2015	**1.5%**	**0.5%**	**2.5%**
	30-39	2009-2015	**1.0%**	**0.8%**	**1.2%**
	40-49	2009-2015	**2.0%**	**1.9%**	**2.2%**
	50-59	2009-2015	**2.7%**	**2.6%**	**2.8%**
	60-69	2009-2015	**1.1%**	**0.9%**	**1.3%**
	70+	2009-2015	**1.6%**	**1.0%**	**2.3%**
	Overall	2009-2015	**1.3%**	**1.3%**	**1.4%**
Distant	0-29	2009-2015	0.0%	0.0%	0.0%
	30-39	2009-2015	0.0%	0.0%	0.0%
	40-49	2009-2015	**2.1%**	**1.3%**	**3.0%**
	50-59	2009-2015	**2.4%**	**1.7%**	**3.2%**
	60-69	2009-2015	**2.3%**	**0.8%**	**3.8%**
	70+	2009-2015	**2.3%**	**0.2%**	**4.5%**
	Overall	2009-2015	**1.4%**	**1.2%**	**1.7%**

[a] Average Annual Percent Change
[b] Lower Confidence Limit (95% Confidence Interval)
[c] Upper Confidence Limit (95% Confidence Interval)

Table 2.6: Average Annual Percent Change (AAPC) in Breast Cancer Incidence Rates/100,000 person-years by hormonal receptor status, age group and year of diagnosis

Hormonal Receptor Status	Agegroup	Years	AAPC[a]	LCL[b]	UCL[c]
ER positive	0-29	2001-2008	-2.4%	-17.5%	15.5%
	30-39	2001-2008	2.5%	-6.0%	11.9%
	40-49	2001-2008	2.9%	-7.5%	14.4%
	50-59	2001-2008	2.1%	-6.0%	10.9%
	60-69	2001-2008	7.4%	-0.5%	15.8%
	70+	2001-2008	9.8%	-3.5%	24.9%
	Overall	2001-2008	4.7%	-3.5%	13.7%
ER negative	0-29	2001-2008	4.5%	-4.8%	14.7%
	30-39	2001-2008	-4.3%	-13.3%	5.6%
	40-49	2001-2008	6.6%	-0.1%	13.7%
	50-59	2001-2008	**11.2%**	**2.5%**	**20.6%**
	60-69	2001-2005	10.6%	-3.6%	26.9%
	70+	2001-2006	8.3%	-7.6%	26.9%
	Overall	2001-2008	**7.6%**	**2.6%**	**12.9%**
PR positive	0-29	2001-2008	9.8%	-9.9%	33.8%
	30-39	2001-2008	7.6%	-2.3%	18.4%
	40-49	2001-2008	8.6%	-4.0%	22.7%
	50-59	2001-2008	7.3%	-1.8%	17.3%
	60-69	2001-2008	**14.1%**	**1.4%**	**8.5%**
	70+	2001-2008	17.9%	-0.8%	40.3%
	Overall	2001-2008	**10.7%**	**0.7%**	**21.7%**
PR negative	0-29	2001-2008	-2.9%	-19.9%	17.9%
	30-39	2001-2008	-7.4%	-14.7%	0.4%
	40-49	2001-2008	4.3%	-3.9%	13.2%
	50-59	2001-2008	7.7%	-2.5%	18.9%
	60-69	2001-2008	**3.9%**	**0.7%**	**7.3%**
	70+	2001-2008	8.4%	-7.4%	26.8%
	Overall	2001-2008	**4.5%**	**1.3%**	**7.8%**

[a] Average Annual Percent Change
[b] Lower Confidence Limit (95% Confidence Interval)
[c] Upper Confidence Limit (95% Confidence Interval)

Table 2.7: Average Annual Percent Change (AAPC) in breast cancer caseloads by Estrogen (ER) and Progesterone (PR) receptor status and age group, predictions from 2009-2015

Hormone Receptor Status	Agegroup	Years	AAPC[a]	LCL[b]	UCL[c]
ER Positive	0-29	2009-2015	0.0%	0.0%	0.0%
	30-39	2009-2015	**1.1%**	**0.7%**	**1.6%**
	40-49	2009-2015	**2.0%**	**1.8%**	**2.2%**
	50-59	2009-2015	**2.7%**	**2.5%**	**2.9%**
	60-69	2009-2015	**1.3%**	**0.9%**	**1.7%**
	70+	2009-2015	**2.0%**	**1.2%**	**2.8%**
	Overall	2009-2015	**1.3%**	**1.3%**	**1.4%**
ER Negative	0-29	2009-2015	0.0%	0.0%	0.0%
	30-39	2009-2015	0.7%	-0.4%	1.8%
	40-49	2009-2015	**2.2%**	**1.9%**	**2.4%**
	50-59	2009-2015	**2.7%**	**2.4%**	**3.0%**
	60-69	2009-2015	**1.1%**	**0.1%**	**2.1%**
	70+	2009-2015	**5.0%**	**1.7%**	**8.3%**
	Overall	2009-2015	**1.4%**	**1.3%**	**1.5%**
PR Positive	0-29	2009-2015	0.0%	0.0%	0.0%
	30-39	2009-2015	**0.8%**	**0.3%**	**1.4%**
	40-49	2009-2015	**2.0%**	**1.7%**	**2.3%**
	50-59	2009-2015	**2.9%**	**2.8%**	**3.0%**
	60-69	2009-2015	**1.3%**	**0.8%**	**1.8%**
	70+	2009-2015	**1.9%**	**1.0%**	**2.9%**
	Overall	2009-2015	**1.4%**	**1.3%**	**1.4%**
PR Negative	0-29	2009-2015	0.0%	0.0%	0.0%
	30-39	2009-2015	**1.5%**	**0.1%**	**3.0%**
	40-49	2009-2015	**2.2%**	**1.9%**	**2.5%**
	50-59	2009-2015	**2.7%**	**2.5%**	**2.9%**
	60-69	2009-2015	**1.0%**	**0.3%**	**1.7%**
	70+	2009-2015	1.3%	-0.8%	3.5%
	Overall	2009-2015	**1.2%**	**1.1%**	**1.3%**

[a] Average Annual Percent Change
[b] Lower Confidence Limit (95% Confidence Interval)
[c] Upper Confidence Limit (95% Confidence Interval)

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Chapter 3

Characterizing Inflammatory Breast Cancer among Arab-Americans in the California, Detroit, and New Jersey Surveillance, Epidemiology and End Results Database, 1988-2008

3.1: Abstract

Inflammatory breast cancer (IBC) is characterized by an apparent geographical distribution in incidence, being more common in North Africa than other parts of the world. Despite the rapid growth of immigrants to the United States from Arab nations, , little is known about disease patterns among Arab Americans because a racial category is rarely considered for this group. The aim of this study was to advance our understanding of the burden of IBC in Arab ethnic populations by describing the proportion of IBC among different racial groups, including Arab Americans from the Detroit, New Jersey and California Surveillance, Epidemiology and End Results (SEER) registries.

We utilized a validated Arab surname algorithm to identify women of Arab descent from

the SEER registries. Differences in the proportion of IBC out of all breast cancer and IBC characteristics by race and menopausal status were evaluated using chi-square tests for categorical variables, t-tests and ANOVA tests for continuous variables, and log-rank tests for survival data. We modeled the association between race and IBC among all women with breast cancer using hierarchical logistic regression models, adjusting for individual and census tract-level variables.

Statistically significant differences in the proportion of IBC out of all breast cancers by race were evident. In a hierarchical model, adjusting for age, estrogen and progesterone receptor, human epidermal growth receptor 2, registry and census-tract level education, Arab-Americans (OR=1.5, 95% CI=1.2,1.9), Hispanics (OR=1.2, 95% CI=1.1,1.3), Non-Hispanic Blacks (OR=1.3, 95% CI=1.2, 1.4), and American Indians/Alaskans (OR=1.9, 95% CI=1.1, 3.4) had increased odds of IBC, while Asians (OR=0.6, 95% CI=0.6, 0.7) had decreased odds of IBC as compared to Non-Hispanic Whites.

IBC may be more common among certain minority groups, including Arab American women. Understanding the descriptive epidemiology of IBC by race may generate hypotheses about risk factors for this aggressive disease. Future research should focus on etiologic factors that may explain these differences.

3.2: Background

Inflammatory breast cancer (IBC) is an aggressive type of breast cancer with poor prognosis. IBC is characterized by an apparent non uniform geographical distribution in

incidence, being more common in North Africa than in other parts of the world. Prior studies have demonstrated that between 1-6% of all breast cancers in the United States are IBC [1-3], while the proportion of IBC in Tunisia has been reported as high as 55% [4] with more recent estimates suggesting that IBC represents 5-7% of all breast cancers in Tunisia.[5]. A population-based study in Egypt established that 11% of all breast cancers there were IBC, which is considerably higher than what is reported in most of the western world [6]. In addition to geographical variability in IBC occurrence, studies also suggest that substantial disparities in IBC occurrence may exist by age, race, and socioeconomic status (SES) [3,7-8]. Studies in the U.S. have demonstrated a higher incidence rate of IBC among African American women as compared to White women, and comparable rates among Hispanic and non-Hispanic white women; moreover, a younger mean age of IBC onset among Hispanic women as compared to White and African American women has been noted [8-10]. Furthermore, socioeconomics may play an important role in IBC risk, as is evident in the rural predominance of the disease in Tunisia where the SES is generally lower than in urban regions [4-5,11], and also in the comparison of IBC in North African migrants to France compared with French women living in the same region [12]. A steady decline in IBC cases has been reported appearing in parallel with improved socioeconomic conditions in Tunisia [13], lending further support for the association between SES and IBC.

Arabic immigrants represent a rapidly growing population in the United States [14,15], although the overall size of the Arab American population is highly debated [16]. While Arab Americans live in all fifty states, it is estimated that the majority reside in California, Michigan, New York, Florida, and New Jersey[17]. Despite the rapid growth

of immigrants from Arab nations, little is known about disease patterns among this group because a racial/ethnic category is often not designated for this group, resulting in broad inclusion of Arabs into the White racial category. Previous studies have constructed and utilized surname databases to identify Arab immigrants and to describe relative proportions of different cancer types among this population [18-20]. A recent study in the Detroit SEER registry demonstrated increased odds of IBC among Arab Americans as compared to European-Americans [21]; however, this estimate failed to reach statistical significance, perhaps due to the small sample size.

The aim of this study was to examine the occurrence of IBC among Arab Americans in the California, Detroit and New Jersey SEER registries. These registries have the largest expected Arab American populations and were included to maximize the number of Arab Americans in our sample. Understanding the descriptive epidemiology of IBC in Arab Americans may generate hypotheses about potential risk factors for this aggressive disease.

3.3: Methods

The study population consisted of all women diagnosed with primary invasive breast cancer from 1988-2008 in the SEER population-based cancer registries in Detroit, New Jersey and California. For each case, the following information from routinely collected registry data was obtained: age at diagnosis, race, hormonal receptor status, tumor characteristics, staging, and survival time. The Reporting Recommendations for Tumor

Marker Prognostic Studies (REMARK) guidelines were followed in the reporting of the hormonal receptor results [22]. Assay results for estrogen and progesterone receptor status, prior to neoadjuvant therapy, if available, were abstracted by the SEER registries from the medical record [23]. Cases where the assay was not performed or was borderline or undetermined were not included in our logistic regression model of marker status by race/ethnicity. The percent of individuals over 25 years of age without a high school diploma within a census tract was also obtained from the SEER registries. We categorized the census-tract level education as high, middle, and low based on tertiles of the overall distribution of this variable in our dataset as follows: High education = <10.85% less than high school graduate; Middle education = >10.85% less than high school graduate and <21.97% less than high school graduate; Low education = >21.97% less than high school graduate. Women 50 years of age and older were considered post-menopausal while those under the age of 50 were considered pre-menopausal. Data were stripped of all personal identifiers, and the analyses were approved by the University of Michigan Institutional Review Board, Wayne State University Human Investigations Committee, the California Protection for Human Subjects Committee, and the Institutional Review Board at the University of Medicine and Dentistry of New Jersey.

Using a validated Arabic name algorithm, we identified Arab American women based on maiden name or surname if maiden name was not available in the National Cancer Institute's SEER registry data from Detroit, New Jersey and California in 1988-2008. The Arabic name algorithm was created by compiling names from vital statistics records that indicated Arab ethnicity, Arab community group name rosters, and other publicly available name lists. There are over 13,000 surnames on the lists and they hvae

been reviewed multiple times by Arab community members for accuracy. Several quality control measures were used in creating the lists [19], and a recent telephone validation survey demonstrated that the lists have a 91% positive predictive value [Schwartz, in press]. This validated surname list was supplied to the SEER registries in our study and a surname match was performed. A de-identified dataset with an Arab (yes/no) variable was returned to our research team for analysis. The SEER race codes and Spanish and Hispanic origin variable based on the direct identification component of NAACCR Hispanic Identification Algorithm were utilized to identify the other racial categories in our study. We then compared the proportion of IBC out of all breast cancers and the tumor characteristics and survival time among Arab American, non-Hispanic White (NHW), non-Hispanic Black (NHB), Hispanic, Asian, and American Indian/Alaskan women.

IBC cases were identified using comprehensive coding including ICD-O 8530, which requires pathologic plugging of the dermal lymphatics with tumor emboli, or the extent of disease (EOD) codes EOD-E70 or EOD-E 710-730 or AJCC T4d. This comprehensive case definition of IBC has been utilized in recent publications on IBC from SEER registries [24, 25].

We evaluated differences in the proportion of IBC out of all breast cancer and IBC characteristics by race and derived menopausal status using chi-square tests or Fisher's exact test for categorical variables and t-tests and ANOVA tests for continuous variables. Log-rank tests were utilized to evaluate differences in IBC survival by race and menopausal status. Logistic regression models were utilized to characterize differences in tumor marker status among the IBC cases by race. We then modeled the

association between race and IBC among all women with breast cancer using hierarchical logistic regression models, adjusting for age, tumor marker status, registry and the derived census tract-level education variable. This model accounts for the hierarchical structure and clustering of the data by specifying random effects for the individual-level and census tract-level variables. Confounders were included in the model based upon our prior knowledge. Furthermore, potential confounders that resulted in at least a 10% change-in-estimate criteria between the crude and adjusted measures were included in the model. We tested for interactions between race and each of the characteristics; significant interactions were retained in the model along with their main effects. The hierarchical logistic model were restricted to the years 1999-2008, where tumor marker status information was more regularly reported in SEER. Data analysis was performed using SAS version 9.0 (SAS Institute Inc, Cary, NC); $P \leq .05$ was used to determine statistical significance.

3.4: Results

A total of 621,465 female breast cancer cases were included in our study population, of which 9,135 (1.47%) were considered IBC. As shown in Table 1, Hispanic women had the lowest mean age at IBC diagnosis of 52.6 years. Arab Americans (58.5 years) and NHW women (60.1 years) were diagnosed with IBC at older ages compared to the other racial groups in our study. Compared to NHW women, all other racial categories were more likely to be diagnosed with IBC tumors that were estrogen receptor (ER) negative and progesterone receptor (PR) negative, and were more likely to be diagnosed when pre-

menopausal (age < 50 years) (Table 1), although this trend was the least pronounced among the Arab American women. Arab Americans had the longest mean IBC survival time of 50.5 months, while American Indian/Alaskan natives had the shortest mean survival of 24.8 months ($p<.0001$). Statistically significant differences in the proportion of IBC out of all breast cancers by racial/ethnic group were evident; 2.91% IBC among American Indian/Alaskan, 2.3% IBC among Hispanics, 2.2% IBC among NHB, 1.7% IBC among Arab Americans, 1.3% IBC among NHW and 1.2% IBC among Asians. (Table 2).

In a hierarchical model, adjusting for age, ER, PR, human epidermal receptor 2 (Her2), registry and census tract-level education, Arab-Americans (OR=1.5, 95% CI=1.2, 1.9), NHB (OR=1.3, 95% CI=1.2, 1.4), Hispanics (OR=1.2, 95% CI=1.1,1.3), and American Indians/Alaskans (OR=1.9, 95% CI=1.1, 3.4) all had increased odds of IBC diagnosis as compared to NHW, while Asians had a decreased odds of IBC as compared to NHW (OR=0.6, 95% CI=0.6, 0.7) (Table 3). Interaction terms for race by each characteristic were evaluated in the hierarchical model. The interaction term for race by ER was statistically significant ($p<.0001$) and was included in the final model. NHW were less likely to have ER/PR negative tumors as compared to all other racial categories, although this difference was not statistically significant among Arab-Americans and American Indian/Alaskan natives (Table 4). Hispanic (45.8%) and American Indian/Alaskan (42.1%) women had the highest percentage of IBC cases diagnosed in the premenopausal years as compared to the other racial groups, while only 26.6% of Arab American women were diagnosed in premenopausal years (Table 5). Premenopausal IBC cases were more likely to be ER/PR negative, and in the low education category as

compared to postmenopausal IBC cases. Further, premenopausal women had a significantly improved mean survival of 96.4 months as compared to 59.2 months among postmenopausal women ($p<.0001$) (Table 5).

3.5: Discussion

This study demonstrated significant differences in the presentation of IBC and the proportion of IBC out of all breast cancers by racial group. Our finding of a younger age at onset of IBC among Hispanic women as compared to NHB and NHW women is consistent with a previous study [9]. Almost half of the IBC cases among Hispanic and American Indian/Alaskan natives occurred before the age of 50. While previous studies suggest that IBC rates are similar between non-Hispanic whites and Hispanic women, we found the proportion of IBC out of all breast cancers was significantly higher among Hispanic women as compared to NHW. If the IBC rates are in fact similar between these women, our results may be explained by differences in the trends of non-IBC breast cancer between groups, as non-IBC breast cancer incidence rates have remained stable after declining 7% from 2002 to 2003 [26, 27]. These findings highlight the limitation of using proportion of IBC out of all breast cancer instead of IBC incidence rates to evaluate racial disparities. If denominator data were available for the Arab population in the SEER geographic areas, we would have been able to calculate age-standardized incidence rates for the racial groups.

The racial disparities in IBC occurrence described in this study may be partially explained by risk factors for IBC that were not adequately controlled for in our analysis. For example, several reproductive factors have been found to be associated with IBC

occurrence in previous studies. IBC patients are reported to have a younger age at menarche and a younger age at first live birth as compared to non-inflammatory breast cancer and non breast cancer patients [4, 7,13, 28-30]. Further, duration of breast feeding exceeding 24 months was found to be significantly associated with IBC in one study [12]. If these reproductive factors are in fact risk factors for IBC and differ by race, as we may suspect [31, 32], it could possibly explain some of the racial disparities in IBC occurrence observed in our study. In addition to reproductive risk factors for IBC, obesity has been shown to be a risk factor for premenopausal IBC but not for postmenopausal non-IBC in one study [33], while another study demonstrated that IBC patients had significantly higher BMI than both non-IBC patients and non-breast cancer patients irrespective of menopausal status [28]. Finally, we utilized census-tract level information on education as a proxy for socioeconomic status, to account for the contextual effect of living in a community with lower educational attainment, since individual-level education and SES information was unavailable in our dataset. According to 2010 Census information, African-Americans and Hispanics have similar rates of poverty, which are approximately threefold greater than Whites [34]. Without detailed information on reproductive factors, obesity and individual-level SES available in the SEER dataset, we cannot control for these factors in our analysis. Therefore, it is possible that some of the difference in proportion of IBC by race may be explained by residual differences in risk factors that are not accounted for in our study.

It has been suggested that the effect of certain risk factors for IBC may differ according to menopausal status [33]. This was apparent in urban-rural differences in IBC cases in Tunisia seen only in premenopausal patients [4], and in obesity as a risk factor

for premenopausal women only [33]. Therefore, we stratified our hierarchical model by derived menopausal status to evaluate whether menopause modified the association between race and IBC. Our derived menopausal status variable has been shown to be a robust indicator of actual menopausal status [35,36], and has been utilized in several population-based studies on breast cancer [37,38]. Stratifying our results for the effect of race on IBC, we found that menopausal status did not significantly modify the effect of race on IBC (data not shown); however, we did find significant differences in disease characteristics between pre-menopausal and post-menopausal IBC cases. The differences in education and hormonal receptor status may provide evidence for differing etiologies for premenopausal and postmenopausal IBC cases, and this should be considered in future research on IBC risk factors. However, it is important to note that we used age as a proxy for menopausal status. Thus, differences in IBC occurrence by menopausal status in our analysis may simply reflect the effect of age and not necessarily an effect of menopause.

Early treatment is critical to improve outcomes for IBC. Our study found improved survival among Arab Americans IBC cases compared to all other racial categories. This finding was also recently reported in non-IBC cases among Arab Americans [21]. American Indian/Alaskan natives were found to have the shortest mean survival time, and efforts to reach these populations for early treatment of disease should become a priority. We also found improved survival times among premenopausal IBC cases as compared to postmenopausal women, which is not entirely surprising due to the implications of age on survival. These survival disparities need to be addressed and may reflect a lack of early detection, lack of timely and aggressive treatment, and access to

care. Without complete treatment information including chemotherapy in our dataset, we are unable to explore these survival differences in more depth in this study.

Limitations of this study include a potential for misclassification of Arab women, especially where the maiden name was unavailable. For example, there is the potential for non-Arab women to be considered Arab based on married surnames, and for differential misclassification between those Arab women identified based on married and maiden surnames. We were unable to assess the magnitude of this potential misclassification bias, as we did not have access to the actual surnames within our dataset. However, we believe that the possibility of misclassification is limited as many Arab ancestry women keep their maiden names upon marriage [39-41], and maiden names are available for a large proportion of the women. Another possible limitation of this study was the lack of information on country of origin or date of immigration to the United States. The Arab American immigrant group is composed of individuals from many diverse Arab nations. Without information on country of origin, we may be missing critical information that could explain disparities in IBC occurrence. We did evaluate the place of birth variable in our dataset, however this variable was missing for 42% of breast cancer cases. Therefore, we were unable to accurately assess this factor in our analysis. Further, we would surmise that immigrants arriving earlier in life would be more likely to experience cancer rates comparable to non-Arab Whites versus immigrants who arrived later [14]. Without information on time of immigration, we may be mixing the effect of IBC occurrence between recent Arab immigrants, who maintain certain cultural norms from their countries of origin, with Arab women who have become acculturated to the Western lifestyle after having been born in or living in the U.S. for a

considerable amount of time. It would be beneficial to evaluate IBC cancer occurrence by time of immigration among migrant groups in the U.S. in order to understand potential environmental risk factors for the disease.

A further limitation could be the use of different laboratories to determine hormonal receptor status in our dataset. Additionally, the hormonal receptor data were not routinely collected during our study period, so we do have to be concerned about missing data for these variables. To overcome this limitation, we restricted our analysis on ER/PR from 1990 forward and on Her2 from 1999 forward, when this information was more regularly reported in the SEER registries. Lack of data on other potentially important covariates including reproductive factors, obesity, individual-level SES, acculturation, and urban/rural status could lead to residual confounding in our analysis. It is also important to consider that our data came from the Detroit SEER, which only includes 3 counties in Michigan, while the California and New Jersey registries are state-wide. This could potentially affect the generalizability of our results if we think that these registries are not representative of the overall population of women with breast cancer in the United States. Finally, this is a purely descriptive analysis and we are unable to draw causal inferences from the results.

Strengths of this study include the use of large-scale population-based SEER registry data, which is considered to be reliable and accurate as it meets International Agency for Research on Cancer (IARC) standards, ensuring a certain degree of data quality and comparability based on a number of factors [42]. Further, the IBC case ascertainment definition used in this study is considered valid and is not as conservative as previous studies requiring the pathological diagnosis of IBC. The name algorithm to

identify Arab ancestry has been constructed and utilized to describe relative proportion of cancer among this population in previous studies [18-20]. Finally, this study is innovative as it maximized the number of Arab Americans represented in the study sample by applying data from California, Detroit, and New Jersey registries.

Our results suggest that IBC occurrence may be more common among certain minority groups, including Arab American women. With the significant lack of epidemiologic data on IBC, this study represents important progress to our understanding of this rare and aggressive disease. By evaluating racial disparities in IBC occurrence, we hope to generate further hypotheses about potentially modifiable risk factors for IBC. Future research should focus on etiologic factors that may underlie these differences and also examine country of origin and date of immigration to the U.S. to further understand potentially modifiable risk factors for IBC.

Figure 3.1: Racial Distribution of IBC Cases (n=9,135)

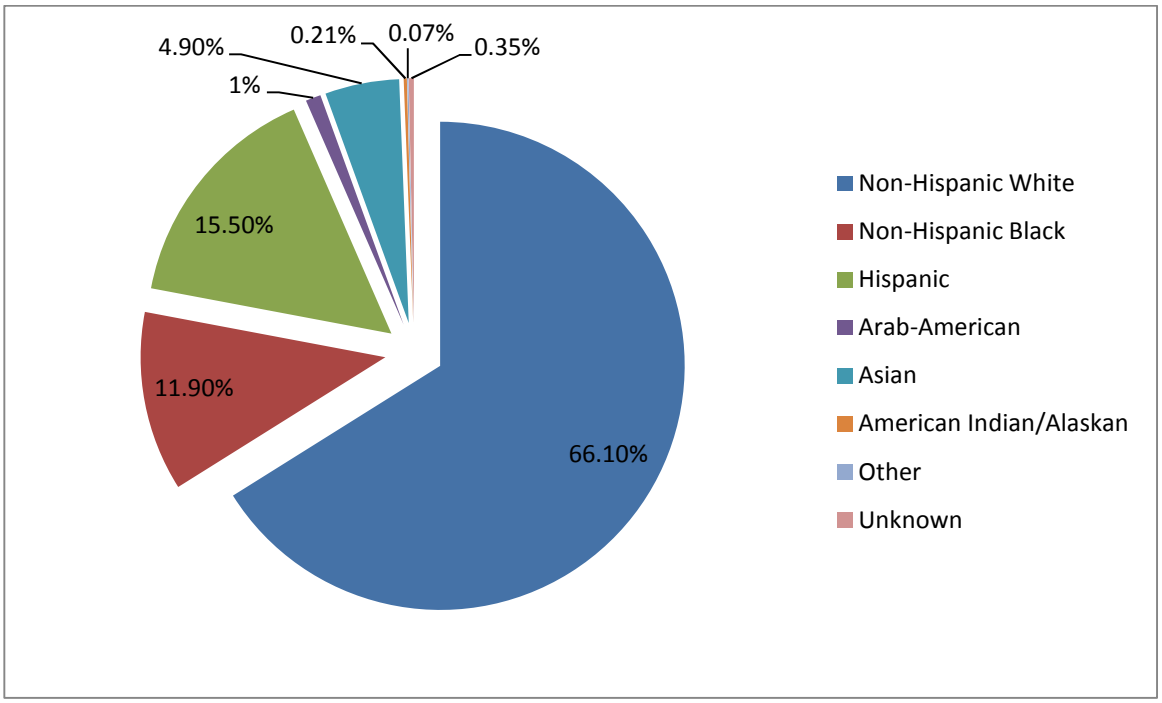

Figure 3.2: Estrogen Receptor (ER) and Progesterone Receptor (PR) Status Distribution of IBC Cases by Race

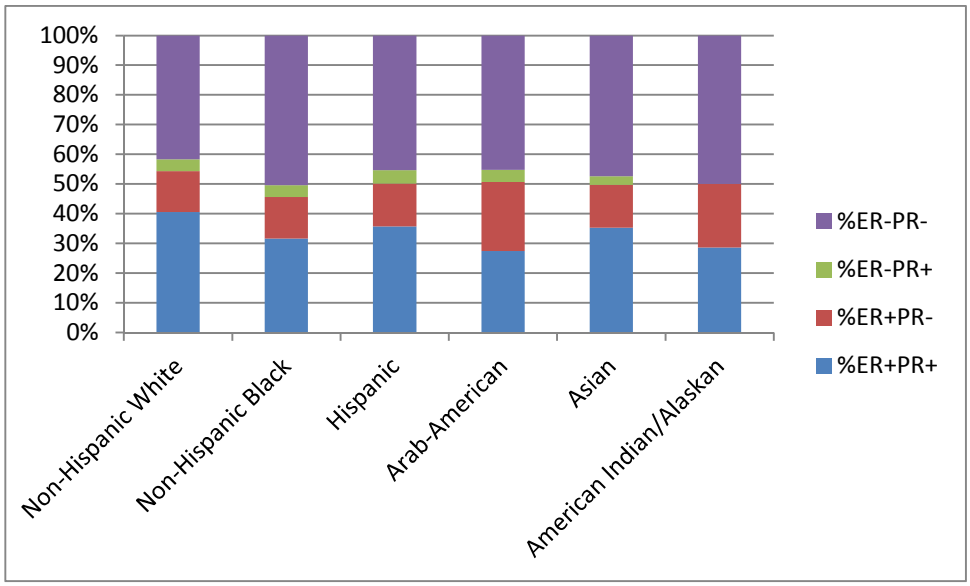

Figure 3.3: Human Epidermal Growth Factor Receptor 2 **(**Her2) Receptor Status Distribution of IBC Cases by Race

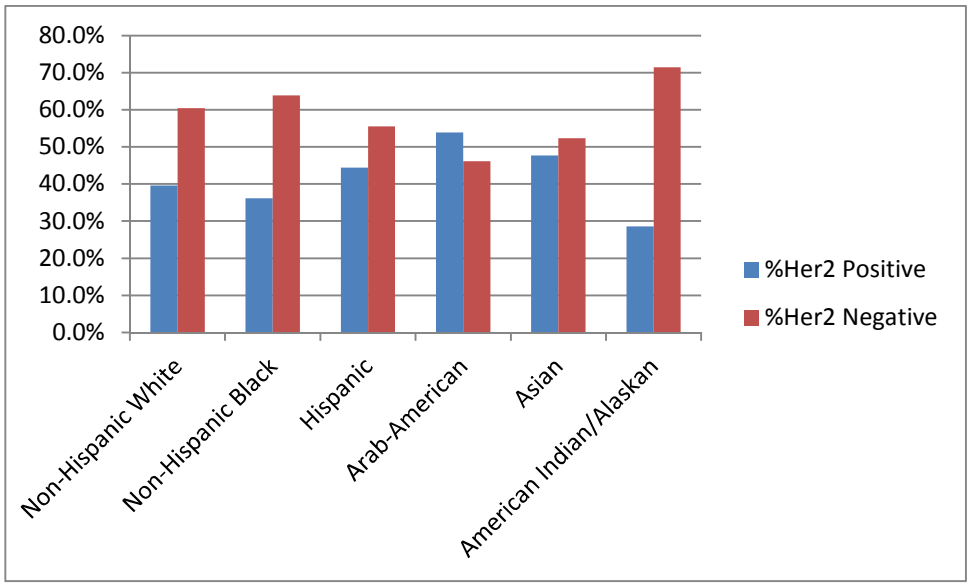

Figure 3.4: Age Distribution of IBC Cases by Race

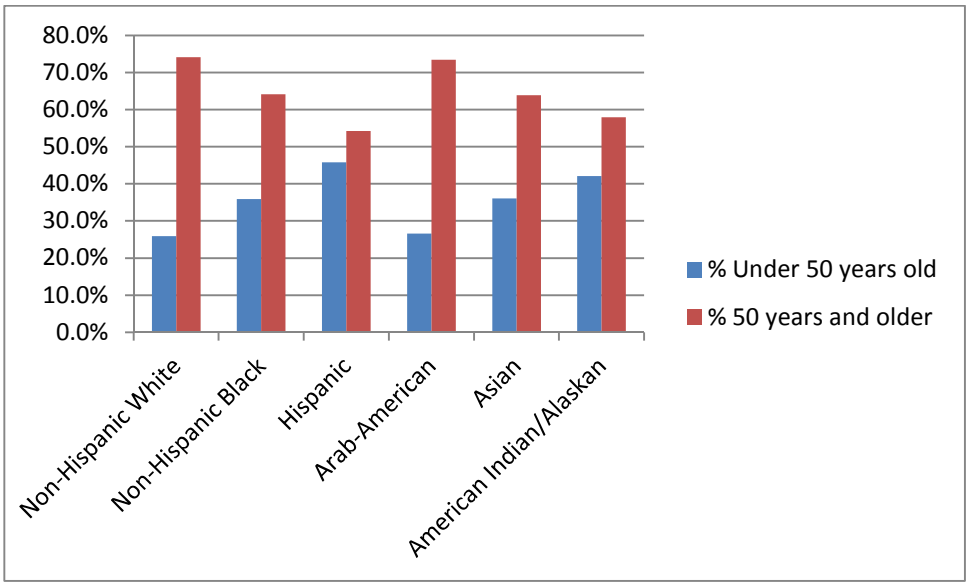

Figure 3.5: Survival Distribution of IBC Cases by Race

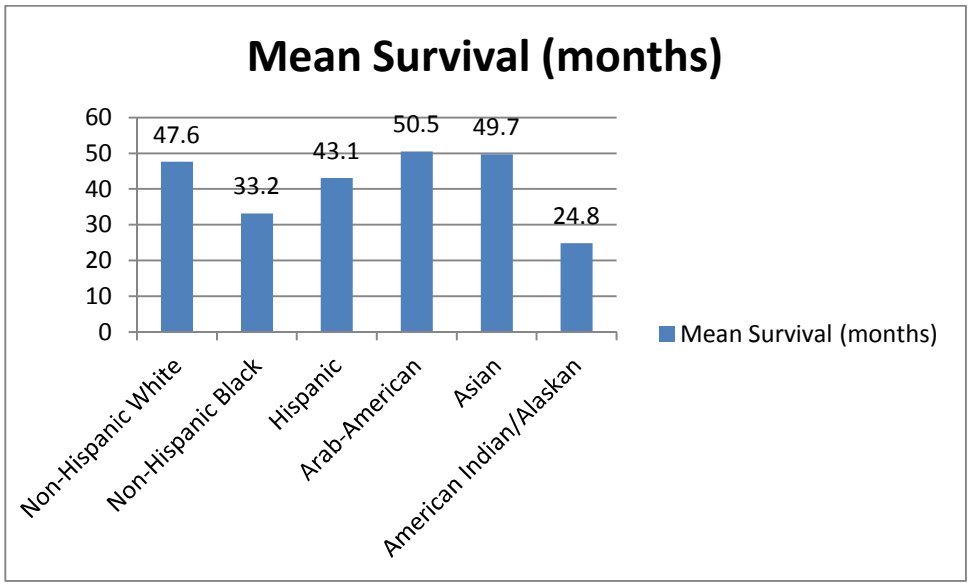

Table 3.1: Inflammatory Breast Cancer Characteristics by Race

	NHW [a] (n=6,035) n (%)	NHB [b] (n=1,085) n(%)	Hispanic (n=1,415) n(%)	Arab (n=94) n(%)	Asian (n=449) n(%)	AI_Al[c] (n=19) n(%)	p-value
Estrogen Receptor [d]							
Positive	2,219 (39.3%)	332 (32.1%)	491 (36.4%)	38 (42.2%)	156 (36.7%)	7 (36.8%)	**0.0070**
Negative	1,833 (32.4%)	391 (37.7%)	474 (35.1%)	36 (40%)	156 (36.7%)	7 (36.8%)	
Unknown	1,598 (28.3)	313 (30.2%)	384 (28.5%)	16 (17.8%)	113 (26.6%)	5 (26.3%)	
Progesterone Receptor [d]							
Positive	1,762 (31.2%)	252 (24.3%)	380 (28.2%)	23 (25.6%)	117 (27.5%)	4 (21.1%)	**0.0003**
Negative	2,195 (38.8%)	453 (43.7%)	570 (42.2%)	50 (55.5%)	189 (44.5%)	10 (52.6%)	
Unknown	1,693 (30%)	331 (32%)	399 (29.6%)	17 (18.9%)	119 (28%)	5 (26.3%)	
Combined Hormonal Status [e]							
ER+ PR+	1,597 (40.6%)	222 (31.6%)	336 (35.7%)	20 (27.4%)	108 (35.3%)	4 (28.6%)	**0.0002**
ER+ PR-	538 (13.7%)	98 (14%)	136 (14.4%)	17 (23.3%)	44 (14.4%)	3 (21.4%)	0.0948
ER- PR+	158 (4.0%)	28 (4%)	42 (4.5%)	3 (4.1%)	9 (2.9%)	0 (0%)	0.8900
ER- PR -	1,642 (41.7%)	354 (50.4%)	428 (45.4%)	33 (45.2%)	145 (47.4%)	7 (50%)	**0.0129**
Her-2 Receptor [f]							
Positive	594 (21.9%)	94 (17.9%)	248 (29.9%)	14 (29.2%)	83 (31.1%)	2(18.2%)	**<0.0001**
Negative	906 (33.4%)	166 (31.7%)	310 (37.3%)	12 (25.0%)	91 (34.1%)	5 (45.5%)	
Unknown	1,209 (44.6%)	264 (50.4%)	272 (32.8%)	22 (45.8%)	93 (34.8%)	4 (36.3%)	
Education [g]							
High	2,233 (37.0%)	183 (16.9%)	198 (14.0%)	36 (38.3%)	128 (28.5%)	3 (15.8%)	**<0.0001**
Middle	2,021 (33.5%)	249 (23.0%)	262 (18.5%)	30 (31.9%)	127 (28.3%)	8 (42.1%)	
Low	1,781 (29.5%)	653 (60.2%)	955 (67.5%)	28 (29.8%)	194 (43.2%)	8 (42.1%)	

	NHW [a] (n=6,035) n (%)	NHB [b] (n=1,085) n(%)	Hispanic (n=1,415) n(%)	Arab (n=94) n(%)	Asian (n=449) n(%)	AI_Al[c] (n=19) n(%)	p-value
Menopausal Status							
Pre (<50 yr)	1,565 (25.9%)	389 (35.9%)	648 (45.8%)	25 (26.6%)	162 (36.1%)	8 (42.1%)	**<0.0001**
Post (≥50 yr)	4,470 (74.1%)	696 (64.1%)	767 (54.2%)	69 (73.4%)	287 (63.9%)	11 (57.9%)	
	mean(sd)	**mean(sd)**	**mean(sd)**	**mean(sd)**	**mean(sd)**	**mean(sd)**	**p-value**
%No Education [g]	17.7 (13)	29.4 (18)	35.2 (21)	18.6 (15)	23.7 (17)	28.8 (18)	**<0.0001**
Age at diagnosis	60.1 (14.6)	56.2 (14.5)	52.6 (14)	58.5 (11.7)	54.0 (12.5)	54.8 (12.7)	**<0.0001**
Survival (months)	47.6 (49.3)	33.2 (37.5)	43.1 (44.2)	50.5 (51.3)	49.7 (47.4)	24.8 (25.7)	**<0.0001**

[a] NHW=Non-Hispanic White
[b] NHB = Non-Hispanic Black
[c] AI_Al = American Indian/Alaskan native
[d] Sample size for ER and PR for cases diagnosed 1990-2008 only (NHW=5650, NHB=1036, Hispanic=1349, Arab=90, Asian=425, AI_Al=19)
[e] Combined hormonal status based only on non-missing data from 1990-2008 (sample size for NHW = 3935, NHB=702, Hispanic =942 , Arab=73, Asian=306, Al_AI=14)
[f] Sample size for HER2 for cases diagnosed 1999-2008 (NHW=1209, NHB=524, Hispanic=830, Arab=48, Asian=267, Al_AI=11)
[g] % No Education (25 years of age or older without a high school diploma) and Education (tertiles of distribution) based on census tract-level information
*ANOVA test for continuous variables, chi-sq for categorical (or Fisher's exact test for cell counts <5), log-rank test for Survival.

Table 3.2: Proportion of IBC out of all Breast Cancers by Race and Registry

Race	All Breast Cancer	IBC	%IBC	p-value
All Races combined	621,465	9,135	1.47%	-
NHW	462,717	6,035	1.30%	**<0.0001**
NHB	49,980	1,085	2.17%	
Hispanic	61,062	1,415	2.32%	
Arab-American	5,539	94	1.70%	
Asian	37,085	449	1.21%	
American Indian/Alaskan	652	19	2.91%	
Other	506	6	1.19%	
Unknown	3,924	32	0.82%	
New Jersey Registry	135,764	1,333	0.98%	**<0.0001**
Detroit Registry	60,412	808	1.34%	
California Registry	425,289	6,994	1.64%	

*P-value from chi square test

Table 3.3: Odds Ratios (95% CI) for IBC by Race

Race	Crude Model	Age-Adjusted	HLM[a]
Non-Hispanic White	1.0 (ref)	1.0 (ref)	1.0 (ref)
Non-Hispanic Black	**1.8 (1.7, 2.0)**	**1.7 (1.6, 1.8)**	**1.3 (1.2, 1.4)**
Hispanic	**1.7 (1.6, 1.8)**	**1.5 (1.4, 1.6)**	**1.2 (1.1, 1.3)**
Arab-American	**1.4 (1.1, 1.8)**	**1.3 (1.1, 1.6)**	**1.5 (1.2, 1.9)**
Asian	**0.9 (0.8, 0.9)**	**0.8 (0.7, 0.8)**	**0.6 (0.6, 0.7)**
American Indian/Alaskan	**2.2 (1.4, 3.5)**	**2.0 (1.2, 3.2)**	**1.9 (1.1, 3.4)**
Other	0.9 (0.3, 2.3)	0.8 (0.3, 2.0)	1.1 (0.3, 3.8)
Unknown	**0.6 (0.4, 0.9)**	**0.6 (0.4, 0.9)**	0.9 (0.6, 1.3)

[a]=Hierarchical logistic regression model adjusted for age, ER, PR, Her2, registry and census tract-level education and included interaction term between race and ER.

Table 3.4: Odds Ratios (95% CI) for Marker Status at IBC Diagnosis by Race

Marker [a]	NHW	NHB	Hispanic	Arab	Asian	AI Al
ER+PR+	1.0	**0.72 (0.61, 0.84)**	**0.87 (0.76, 0.99)**	0.75 (0.46, 1.2)	0.88 (0.7, 1.1)	0.74(0.25, 2.2)
ER- PR-	1.0	**1.30 (1.1, 1.5)**	**1.16 (1.02, 1.3)**	1.45 (0.9, 2.2)	**1.28 (1.04, 1.57)**	1.56 (0.6, 4.0)

[a] ER and PR non-missing data from 1990-2008 only (sample size for NHW = 3935, NHB=702, Hispanic =942 , Arab=73, Asian=306, Al_AI=14)

Table 3.5: Study Population Characteristics of IBC cases by Menopausal Status (age <50 yr vs. >=50 yr)

	All IBC (n=9,135)		Premenopausal IBC (n=2811)		Postmenopausal IBC (n=6,324)		p-value
	n	(%)	n	(%)	n	(%)	
Race							
Non-Hispanic White	6,035	(66.1%)	1,565	(25.9%)	4,470	(74.1%)	**<0.0001**
Non-Hispanic Black	1,085	(11.9%)	389	(35.9%)	696	(64.1%)	
Arab-American	94	(1%)	25	(26.6%)	69	(73.4%)	
Hispanic	1,415	(15.5%)	648	(45.8%)	767	(54.2%)	
Asian	449	(4.9%)	162	(36.1%)	287	(63.9%)	
American Indian/Alaskan	19	(0.2%)	8	(42.1%)	11	(57.9%)	
Other	6	(0.07%)	1	(16.7%)	5	(83.3%)	
Unknown	32	(0.35%)	13	(40.6%)	19	(59.4%)	
Estrogen Receptor [a]							
Positive	3,258	(37.9%)	893	(33.8%)	2,365	(39.7%)	**<0.0001**
Negative	2,909	(33.8%)	1,017	(38.4%)	1,892	(31.7%)	
Unknown	2,438	(28.3%)	735	(27.8%)	1,703	(28.6%)	
Progesterone Receptor [a]							
Positive	2,551	(29.7%)	768	(29.0%)	1,783	(29.9%)	0.17
Negative	3,480	(40.4%)	1,109	(41.9%)	2,371	(39.8%)	
Unknown	2,574	(29.9%)	768	(29.0%)	1,806	(30.3%)	

	All IBC (n=9,135)		Premenopausal IBC (n=2811)		Postmenopausal IBC (n=6,324)		p-value
Her-2 Receptor [b]							
Positive	1,042	(23.6%)	349	(27.3%)	693	(22.1%)	**0.0005**
Negative	1,496	(33.9%)	426	(33.4%)	1,070	(34.1%)	
Unknown	1,879	(42.5%)	502	(39.3%)	1,377	(43.8%)	
Education [c]							
High	2,801	(30.7%)	814	(29.0%)	1,987	(31.4%)	**<0.0001**
Middle	2,702	(29.6%)	756	(26.9%)	1,946	(30.8%)	
Low	3,632	(39.8%)	1,241	(44.2%)	2,391	(37.8%)	

	mean	(sd)	mean	(sd)	mean	(sd)	p-value
% No Education [c]	22.1	(17)	24.1	(18.4)	21.2	(16.3)	**<0.0001**
Age at diagnosis	58.1	(14.7)	41.7	(5.8)	65.4	(11.2)	**<0.0001**
Survival time in months	46.5	(122.2)	96.4	(77.3)	59.2	(61.1)	**<0.0001**

[a] Sample size for ER and PR for cases diagnosed 1990-2008 only (IBC=8,605, pre-menopause=2,645, post-menopause =5,960))
[b] Sample size for HER2 for cases diagnosed 1999-2008 (IBC=4,417, pre-menopause=1,277, post-menopause =3,140)
[c] % No Education (25 years of age or older without a high school diploma) and Education (tertiles of distribution) based on census tract-level information
* ANOVA test for continuous variables, chi-sq for categorical (or Fisher's exact test for cell counts <5), log-rank test for Survival. All statistical tests comparing differences in premenopausal and postmenopausal IBC cases

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Chapter 4

Comparison of Criteria to Identify Inflammatory Breast Cancer from Medical Records and the Surveillance, Epidemiology and End Results Database, 2007-2009

4.1: Abstract

Inflammatory breast cancer (IBC) is a relatively rare and extremely aggressive form of breast cancer that is diagnosed clinically. Standardization of clinical diagnoses is challenging, both nationally and internationally; moreover, IBC diagnostic criteria have changed over time. This study aimed to compare diagnostic factors of IBC reported in a US Surveillance, Epidemiology, and End Results (SEER) registry to clinical criteria found in the medical records of all invasive breast cancer cases at a single institution.

We conducted a medical record review of all female invasive breast cancers (n=915) seen at an NCI comprehensive cancer center in Detroit from 2007-2009. IBC cases were identified based on the presence of the main clinical characteristics of the disease (erythema, edema, peau d'orange). We compared the proportion of IBC out of all breast cancers, using these clinical criteria and the standard SEER IBC codes.

In the reviewed cases, the clinical criteria identified significantly more IBC cases (n=74, 8.1%) than the standard IBC SEER definition (n=19, 2.1%) (P<.0001). No IBC cases were identified in the cancer center records using the SEER pathological coding, which requires the diagnosis of inflammatory carcinoma on the pathology report, a notation that is rarely if ever made.

Emphasis must be placed on the documentation of clinical and pathological characteristics of IBC in the medical record, so that analysis of putative IBC subtypes will be possible and we can further evaluate and come to a consensus on the definition of IBC to be utilized in future research.

4.2: Background

Inflammatory breast cancer (IBC) is the most aggressive and deadly form of breast cancer [1], with nearly twice the risk of death as compared to locally advanced breast cancer [2,3]. Treatment in the form of combination chemotherapy should be initiated urgently to improve survival, which is in peril if treatments are delayed by weeks to months. Therefore, accurate and prompt diagnosis is paramount. Despite its name, IBC is not observed to be associated with a profuse cellular inflammatory response at the time of diagnosis, although this does not preclude that inflammatory events may play a role in its etiology. In fact, the characteristic redness and swelling of the breast in IBC that in many cases may resemble inflammation, are due to the lymph ducts being clogged with tumor cells, a process termed dermal lymphatic invasion by tumor emboli [4,5]. The diagnosis of IBC has changed over time to include different clinical and pathological

characteristics of the disease. Currently, a clinical IBC diagnosis is made when the history and physical examination document the rapid onset (weeks to months, not years) of the characteristic skin features and a biopsy of the breast, or of the affected skin of the breast, shows carcinoma [6-8]. However, the main clinical symptoms (erythema, edema, and peau d'orange) and pathologic characteristics (dermal invasion of breast lymphatic ducts by tumor cells) of IBC are not uniformly observed in quantity and/or severity among patients with IBC. Therefore, in practice, by using a combination of clinical and pathological criteria, IBC cases can be identified in different ways for different patients [9]. Furthermore, potential subtypes of IBC may exist based on the presence or absence of these clinical and pathological characteristics. The use of differing criteria for IBC diagnosis – and the relative rarity of the disease – has hampered epidemiologic research on IBC, making it difficult to obtain adequate representative samples of IBC cases and to compare results across studies.

The identification of IBC in the Surveillance, Epidemiology, and End Results (SEER) registry data has varied over time. Historically, IBC cases were assigned according to the pathological codes (International Classification of Diseases for Oncology (ICD-O code 8530)) [10] specifically reserved for IBC with tumor invasion of dermal lymphatic ducts (DLI). However, a new rule implemented in 2007 states that the ICD-O histology code 8530 for IBC should only be used "when the final diagnosis of the pathology report specifically states inflammatory carcinoma." Even if the final diagnosis shows infiltration of dermal lymphatics, but the words "inflammatory carcinoma" are not included in the final pathology report, the rules state it should not be coded to the 8530 code [11]. Additionally, an American Joint Cancer Committee (AJCC) Stage "T4d"

variable has been designated in SEER for IBC described as "a clinicopathologic entity characterized by diffuse erythema and edema (peau d'orange) of the breast, often without an underlying mass involving the majority of the breast" for cases beginning in 2004 [12]. More recently, IBC cases have been identified in the SEER registry using either the AJCC T4d variable or the Extent of Disease (EOD) variables, which record a combined clinical and pathologic assessment of disease abstracted from the pathology report [9]. The EOD codes allow for stratification by extent of clinical characteristics. A detailed report of the EOD codes 600, 710, 715, 720, 725, 730, 750, and 780 for assigning possible IBC cases are described in a SEER report of 2009 [13]. A standard IBC definition of either AJCC T4d or EOD 710-730 or pathological ICD-O 8530 has recently been advocated to identify IBC cases (2004+) from the SEER registries [14, 15].

The ensuing complexities of coding the IBC diagnosis in registries, which stems from IBC's unique and unusual presentation, makes comparing incidence of IBC between countries extremely challenging due to the lack of a standardized case definition and uniform diagnostic criteria. Furthermore, there does appear to be a significantly heterogeneous global distribution in IBC occurrence. Based on SEER data, between 1% and 6% of all patients with breast cancer in the United States have IBC [16-18]. However, in Tunisia, up to 55% of breast cancer cases have been reported as IBC [19], while more recent estimates describe IBC in Tunisia as 5-7% of breast cancer cases [20]. In some low- and middle- income countries (LMIC), it has been noted that IBC may not be documented in cancer registries, despite clinical characteristics of IBC being evident in the medical records. To address this limitation, in a collaborative effort between US and LMIC researchers, a comprehensive checklist of symptoms, signs, and clinical

characteristics suggestive of IBC was developed to facilitate and standardize abstraction of information from medical records [7,8]. IBC cases were then identified using the simplified clinical definition of erythema, edema, and peau d'orange as its three main clinical features: most-likely IBC exhibited all three features, possible IBC cases had any two of the three signs or had peau d'orange only, and non-IBC cases had edema only, erythema only, or none of these three clinical features. Using this clinical criterion to define IBC cases, a population-based study demonstrated that 11% of all breast cancers in Egypt are likely IBC, which is unequivocally higher than what is currently reported in the U.S. and most western countries where data are available [21].

Regional variations in IBC may thus reflect differences in diagnostic tools, disease definition, or true differences in occurrence due to varying levels of risk factors by region. Identical criteria for the identification of IBC cases would greatly facilitate comparative studies. In addition to facilitating epidemiologic studies, this issue is of particular clinical and humanitarian importance in IBC because survival is so tied to prompt initiation of chemotherapy treatment. Neither primary surgery nor radiotherapy have been shown to be effective as initial therapies and even minor delays in initiation of chemotherapy likewise vastly diminish its beneficial effects. The specific aim of this study was to ascertain the number of IBC cases at a single institution in Detroit, Michigan for a 3-year period (2007-2009) using clinical criteria to identify IBC cases. By applying an identical case ascertainment system as was used in Egypt to medical records in the United States, we hypothesized that we can provide evidence to support a more accurate process to capture the burden of IBC in the United States. As a corollary, we surmised that we would also be able to establish a means for comparisons between the burden of

IBC relative to total breast cancer in Egypt and the US. [21,22]. Furthermore, we compared the IBC cases identified by the clinical criteria to what is documented in the SEER registry in order to determine whether IBC is being ascertained at equivalent levels using SEER case definitions at a major cancer hospital, which provides cases to the Detroit SEER registry.

4.3: Methods

For this study, we conducted a medical record review of all female invasive breast cancer cases over 20 years of age seen at an NCI comprehensive cancer center in Detroit, Michigan from 2007-2009. The center is a tertiary cancer center dedicated to oncology care and research. Patients are often self-referred, referred from their primary physicians or specialists, or from smaller hospitals or clinics to the tertiary facility for surgery, consultations with specialists, and for short- and long-term patient care. As is true of all tertiary care centers in the US, it is assumed that this comprehensive cancer center's patient population experiences a larger than average complexity of disease. This site was chosen due to the large patient volume, the availability of clinical resources, including electronic medical records, catchment within a SEER registry, and existing collaborations that facilitated coordination of the medical record review. Patients were eligible for the study if they had received all or part of their breast cancer diagnosis and/or treatment at the cancer center. We excluded 1 patient who was seen only for part of her diagnostic workup, 34 patients who were treated only for a recurrence or persistence of disease, and 12 patients where this information was missing. These patients were excluded out of

concern that adequate information would not be documented in the medical record. In order to be confident that all available clinical information for our study was documented in the electronic records, we reviewed the paper medical charts for a subset of our sample (n=23), including cases from each year of our study and those with varying amount of diagnosis and treatment performed at the cancer hospital. We found new information on tumor size and hormone receptor status for one patient in the paper records. Since this type of information was not the focus of our analysis, we are confident that our application of the clinical criteria to the electronic records was sufficient in documenting the clinical characteristics of IBC from the record. The final sample for our record review comprised 915 invasive breast cancer cases.

For eligible cases, information was extracted from the records regarding clinical and pathological characteristics of the disease at diagnosis. Age, menopausal status, weight, height, tumor molecular characteristics (estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (Her2) expression), imaging, and treatment were recorded. Tumor size measurements were extracted from clinical reports based on the size of the palpable mass when information was available. We identified IBC cases according to the documentation of the main clinical characteristics of IBC in the record; erythema (redness), edema (swelling), and peau d'orange (dimpling). We then compared differences in the number of IBC cases identified by the clinical criteria (possible and most likely IBC) with the pathologic (ICD-O 8530) and the standard SEER criteria (ICD-O 8530 or EOD 710-730 or AJCC 6th edition staging T4d). Further, to be more certain that the cases being identified by the clinical criteria were truly IBC, we calculated the number of IBC cases based on a more stringent criterion of

clinical IBC as well as treatment with neoadjuvant chemotherapy, this being a hallmark of IBC (but not exclusive to IBC).

Next, we tested whether there were statistically significant differences in the proportion of IBC cases identified using the standard SEER coding systems and the clinical criteria, using the McNemar's test. This non-parametric test accounts for the correlated nature of our sample by determining whether the marginal proportions differed between groups. Differences in characteristics between IBC and non-IBC cases, and in the presence of clinical symptoms of IBC within categories of clinical diagnosis, were examined using chi-square tests and Fisher's exact test for categorical data and t-tests for continuous variables. Further, we utilized chi-square tests, t-tests and logistic regression models to assess tumor characteristics associated with pathological evidence of disease (DLI). An alpha level of 0.05 was used to determine significance and all test statistics were two-sided. An EpiInfo v3.5.3 database was used to record information from the medical records. Statistical analysis was conducted in both the EpiInfo and SAS (version 9; SAS Institute, Cary, NC) platforms. This study was approved by Wayne State University's Human Investigation Committee and the Institutional Review Board at the University of Michigan.

4.4: Results

Of the 915 breast cancer cases reviewed, the clinical diagnostic criteria identified significantly more IBC cases (n=74, 8.1%) than the standard SEER definition (n=19, 2.1%) ($p<.001$) (Table 1). Using the more stringent criteria to define likely IBC as cases treated with neoadjuvant chemotherapy and documenting the clinical characteristics of

disease, 5.5% of all breast cancers would be considered IBC (Table 1). The SEER pathological criteria, which are dependent on the diagnosis of inflammatory carcinoma being explicitly stated on the pathology report (presumably due to findings of DLI), failed to identify any cases of IBC among the 915 breast cancer cases reviewed (Table 1). Of the 19 IBC cases identified by the standard SEER criteria, 15 (79%) were also identified as IBC by the clinical criteria. However, only 15 (20.3%) of the 74 IBC cases identified by the clinical criteria were also identified as IBC by the standard SEER definition.

According to both the clinical and standard SEER IBC diagnostic criteria, IBC cases were likely to have a larger mean tumor size, and be Her2 positive as compared to non-IBC cases (Table 2). IBC cases were more likely to have DLI noted in the record as compared to non-IBC cases, though this difference was not statistically significant for the IBC cases defined according to the clinical criteria (Table 2). Only 35.1% of the IBC cases identified by the clinical criteria referenced IBC in the medical record, while 84.2% of the cases identified by the standard SEER criteria referenced IBC (Table 2).

The clinical criteria specified 8 cases (0.9%) that were most likely IBC as they presented all three characteristics (erythema, edema, peau d'orange). DLI was documented for 12.5% of the "Most likely IBC," 3% of the "Possible IBC," and 1.4% of the "Not IBC" according to the clinical criteria (p=.03) (Table 3). We found no significant differences between breast cancer cases with and without DLI in regards to age, Her2 receptor status, menopausal status, race/ethnicity or in anthropometric measures of weight and height (Table 4). Cases with DLI noted in the record did appear to have larger mean tumor size, were more likely to present with erythema, edema,

angiolymphatic invasion, and ulcerations, and were more likely to be ER negative and PR negative as compared to cases without DLI (Tables 4 and 5). Of the 74 cases considered IBC according to the clinical criteria, only 3 cases were noted to have DLI in the record. Furthermore, only 3 of the 19 IBC cases according to the standard SEER IBC definition noted the presence of DLI in the record. Thus, most of the 15 breast cancer cases with DLI noted in the record were not considered to be IBC according to either definition.

Of the 74 cases considered IBC according to the clinical criteria, 59 of these cases were not considered IBC according to the standard SEER IBC definition. As depicted in Table 6, 57.6% of these discrepant IBC cases were localized tumors, 71.2% were of ductal histology and most were considered AJCC 6th edition T2 (27.1%) or T4b (23.7%). Of the 50 IBC cases that presented with the main clinical characteristics of disease and received neoadjuvant chemotherapy, 28% were coded in SEER as localized tumors, 68% were of ductal histology and most were either AJCC 6th edition T4b (24%) or T4d (26%).

4.5: Discussion

IBC is an unusual form of breast cancer with strong and obvious signs and symptoms. Therefore, IBC has been diagnosed clinically and that is still the case today. The reporting of DLI in pathology reports has been unreliable. Moreover, it is reasonable to pose that the emphasis on clinical diagnosis of IBC that has prevailed since the introduction of the AJCC criteria may have led pathologists to largely abandon the documentation of dermal lymphatic invasion (DLI) and IBC in the pathology report. Thus, most IBC cases diagnosed on or after January 1, 2007 will not be identifiable in the SEER registries using the 8530 histology code [23]. Therefore, it is not entirely

surprising in our study that we failed to identify any IBC cases from 2007-2009 coded to histology 8530. It is important to note that the difficulty of consistently identifying IBC cases from the registry as described in this study, are largely due to the coding changes implemented in SEER around IBC. While our review did identify 1.6% of cases with mention of DLI, no cases were coded to the 8530 SEER coding, probably because they did not specifically mention IBC on the pathology report. Future registry studies on IBC need to be aware of these coding complications, as the historically conservative approach to identifying IBC cases from SEER will not be effective for data from 2007 forward.

The importance of DLI in IBC diagnosis remains controversial. Some experts prefer a pathologic definition of IBC inferring that DLI is required for IBC diagnosis [24, 25]. There is also a suggestion that pathologic confirmation of DLI could represent extent of disease, with earlier cases having less DLI [26]. Thus, the DLI may precede the clinical manifestation of IBC. However, when utilizing cancer registries, reliance on DLI for diagnosis may lead to profound underestimation of IBC incidence [23]. IBC is considered a clinical entity with DLI, if present, providing pathological proof, which can only help confirm but its absence cannot negate the diagnosis [27]. Therefore, it is now generally accepted that despite DLI being evident in as many as 50-75% of cases, this finding is not required for the IBC diagnosis [16, 28-29]. The reason for this is simple: if a patient presents with erythema and peau d'orange of several weeks duration and a biopsy reveals cancer, that patient needs urgent chemotherapy as she has, unequivocally, IBC, regardless of whether a cluster of tumor cells was observed in the dermal lymphatics of the particular sample that was obtained and whether this observation was explicitly stated in the pathology report. To delay therapy would endanger this patient's

life. Therefore, the diagnostic criteria, which are meant to be useful to accurately identify IBC cases so the patients can be treated most effectively, need to be informed not just by the clinical reality of the presentation of the disease (e.g. the symptoms and signs), but also by the practical urgency of the treatment, in light of the poor prognosis if treatment is delayed.

In our study sample, tumor characteristics differed between cases with and without DLI, suggesting potential etiologic subtypes of IBC based on the presence of DLI. A study of prognostic factors in IBC found no prognostic value for the diagnostic selection group (clinical or pathologic definition), suggesting that either definition is justified to diagnose IBC [30]. However, in a meta-analysis, Kim et al found that the main cause of differences in treatment outcomes was the variable criteria used across studies to identify IBC [31]; in other words, the manner in which the disease is classified at the time of diagnosis has implications for treatment and prognosis. Furthermore, SEER data suggest that patients with clinical but no pathologic features of IBC have a better prognosis than those with pathologic evidence of IBC. Patients receiving chemotherapy, surgery and radiation therapy with both clinical and pathologic evidence of IBC had a 3-year survival rate of 34% compared with 60% for patients with only clinical features of IBC and 52% for those with only pathologic diagnosis [16]. Thus, depending on the presence or absence of certain characteristics, subtypes of IBC may exist with different prognosis. Therefore, it is imperative that pathological evidence of disease continue to be documented explicitly in the pathology reports at diagnosis along with reference to IBC if suspected, so that potential subtypes of IBC based on the presence or absence of DLI can be further investigated. The ability to distinguish IBC by

the presence or absence of DLI is critical to our understanding of the etiology of this heterogeneous disease.

Utilizing only the clinical criteria at a comprehensive cancer center in Detroit, Michigan from 2007-2009, we found that 8.1% of breast cancers were IBC. These results suggest for the first time, that the incidence of IBC is likely to be significantly underestimated in the US. There is an excess in the proportion of IBC out of all breast cancers in Egypt compared to the US, but our results now show that such difference is not as large as the one found when standard SEER IBC diagnosis was used for the US incidence figures. By comparing the proportion of IBC out of all breast cancers, the differences between countries may be impacted by the differences in the total number of non-inflammatory breast cancer cases in the denominator of the proportion. Future studies should directly compare the age-specific incidence rates of IBC between countries in order to further evaluate absolute differences in IBC rates between countries. Furthermore, it is important to keep in mind that our results are based on a hospital record review at a comprehensive cancer center and not a population-based sample. Women who received care at the cancer center were more likely to have aggressive disease, with more serious prognoses and therefore would have been more readily referred to a tertiary facility; for all these reasons, this hospital-based group would be predicted to exhibit higher stage at diagnosis when compared to the rest of the metropolitan Detroit area (data not shown). Thus, while we found the proportion of IBC out of all breast cancers to be higher at this comprehensive cancer center, this may not be true in a US population-based sample. Furthermore, our ability to apply the clinical criteria for IBC case identification is predicated on the quality of the medical records. If the quality of the medical records

varies significantly between countries, we will still be limited in our ability to draw conclusions on global differences in IBC occurrence. However, hospital medical records are typically considered accurate and adequate for use in epidemiologic research of this kind, and the clinical diagnostic criteria used in this study have been successfully applied to medical records in a previous study [21].

International studies have indicated that ER positive tumors are more prevalent in developed countries compared to LMIC [32]. Although one may speculate that the higher proportion of IBC in North Africa might simply be a reflection of the excess in ER negative tumors in this region since IBC is often ER negative [8, 32-35], there is no basis for this relationship, as IBC has not been found to be present at a constant proportion of all ER negative breast cancers anywhere else in the world. Indeed, in other areas of the developing world, where we might also expect a greater proportion of ER negative breast tumors, the same high proportion of IBC as seen in Egypt has not been reported. IBC cases in Egypt do appear to have a distinct molecular and clinical presentation as compared to IBC in US. One study found that erythema, edema, and peau d'orange were found in 77% of Egyptian patients as compared with 29% found in the US patients (p=.02) and that the number of tumor emboli was significantly higher in tumors from Egypt (mean +/-SD, 14.1 +/-14.0) than in the tumors from the US (mean +/-SD, 5.0+/-4.0), (p=.001) [36]. These differences may be due in part to different etiologic factors of IBC in Egypt from the US or the more aggressive nature of IBC in Egypt compared to the US. If Egyptian cases do present with more clinically apparent disease, it could explain the excess in proportion of IBC out of all breast cancers. These findings support the

theory that IBC is a heterogeneous condition, which varies in presentation and perhaps in etiology by region.

To our knowledge, this is the first study to utilize the precise IBC clinical criteria used in our previous work in Egypt to calculate the proportion of IBC out of all breast cancers at a cancer center in the United States, for the purpose of improving our understanding of global variation in the occurrence of IBC. The study was not designed to validate the clinical criteria or advocate for the clinical definition of IBC; rather, it allowed us to use an identical system to ascertain IBC cases in global comparative analyses. Further, this study highlights the lack of standardization in defining IBC and stresses the importance of understanding these limitations when comparing results across studies. There is a wide variation in symptom presentation in IBC, and most of the clinical characteristics associated with IBC are nonspecific [37]. In our study, due to this non-specificity of the clinical characteristics of IBC, cases appearing to be locally advanced and neglected breast cancers were being identified as IBC. Therefore, relying on a clinical diagnosis of IBC can lead to a wide variability in reporting and presents serious challenges for researchers [17]. The consensus among experts is that the non-specificity of the current clinical diagnostic criteria, coupled with the recognition that many women with IBC are misdiagnosed with mastitis, are the primary causes of delayed diagnosis and management of this aggressive disease [38]. Furthermore, the lack of standards for the time course of symptoms adopted by some groups later than 2007 may have also contributed to the confusion between IBC and non-IBC locally advanced breast cancers.

We conclude that relying on varying systems of IBC identification to compare incidence across regions should be avoided. By applying the exact clinical criteria utilized in this study to medical records from different regions, we are at least avoiding the discrepancy in differing criteria for diagnosis of IBC across studies. Inclusion of the clinical criteria in identifying IBC from medical records will increase the detection of IBC cases, which may lead to improved patient care. However, it should be stressed that the clinical criteria alone due to their relative non specificity are not meant to be used in isolation of the biopsy, which is, in fact, a requirement for cancer diagnosis of any type. What we have come to know as IBC may differ from the disease that was historically reported in younger women based on anecdotal data, was more often associated with pregnancy, and histologically characterized by presence of DLI. Given the current SEER codification rules, this study demonstrates that our ability to identify IBC through the explicit diagnosis being written on the pathology report is very close to zero. Emphasis must be placed on the documentation of clinical and pathological characteristics of IBC in the medical record, so that analysis of putative IBC subtypes will be possible and we can further evaluate and come to a consensus on the definition of IBC to be utilized in future research. The findings of this study add to our understanding of the global variation in IBC incidence and have important implications for diagnosis, treatment, prognosis and future research on IBC.

Table 4.1: Comparison of Different Criteria and SEER coding for Identification of IBC Cases out of 915 Invasive Breast Cancer Cases from 2007-2009

IBC Criteria	IBC Count	% IBC	p-value
Main IBC Criteria			
Clinical	74	8.1%	<.0001
Standard	19	2.1%	
IBC SEER coding			
AJCC T4d	19	2.1%	
EOD-E 600	0	0.0%	
EOD-E 710	10	1.1%	
EOD-E 715	0	0.0%	
EOD-E 720	0	0.0%	
EOD-E 725	1	0.1%	
EOD-E 730	7	0.8%	
EOD-E 750	1	0.1%	
EOD-E 780	0	0.0%	
Histology 8530	0	0.0%	
Other IBC Criteria			
Clinical + Neoadjuvant Chemo	50	5.5%	
Standard + clinical criteria	15	1.6%	
Standard only	4	0.4%	
Pathologic only	0	0.0%	

Clinical = Any two signs of erythema, edema, peau d'orange or peau d'orange alone
Standard = ICD-O 8530 or EOD-E 710-730 or AJCC 6th edition T4d
Clinical + Neoadjuvant = Any two signs of erythema, edema, peau d'orange or peau d'orange alone AND received neoadjuvant chemotherapy
Pathologic = ICD-O 8530
P-value for difference between Clinical and Standard criteria based on McNemar test

Table 4.2: Descriptive statistics of Invasive Female Breast Cancer Cases (n=915) from Medical Records Diagnosed from 2007-2009 at a Single Institution

	All (n=915)	Clinical IBC			Standard IBC		
		IBC (n=74)	non-IBC (n=841)	p	IBC (n=19)	non-IBC (n=896)	p
Mean age (years)	57.4	57.2	57.4	0.92	59.0	57.4	0.60
Mean tumor size (cm)	3.2	6.2	2.9	**0.00**	8.4	3.1	**0.00**
IBC mentioned (%)	3.4%	35.1%	0.6%	**0.00**	84.2%	1.7%	**0.00**
Derm lymph inv (%)	1.6%	4.1%	1.4%	0.11	15.8%	1.3%	**0.00**
ER							
ER positive (%)	64.8%	59.5%	65.3%	0.19	57.9%	65.0%	0.60
ER negative (%)	33.1%	40.5%	32.5%		42.1%	32.9%	
Unknown (%)	2.1%	0.0%	2.3%		0.0%	2.1%	
PR							
PR positive (%)	55.1%	56.8%	54.9%	0.41	63.2%	54.9%	0.67
PR negative (%)	42.7%	43.2%	42.7%		36.8%	42.9%	
Unknown (%)	2.2%	0.0%	2.4%		0.0%	2.2%	
Her2							
Her2 positive (%)	16.9%	23%	16.4%	**0.04**	47.4%	16.3%	**0.00**
Her2 negative (%)	77.6%	77%	77.6%		47.4%	78.2%	
Unknown (%)	5.5%	0%	6.0%		5.2%	5.5%	
Menopausal status							
Pre-menopausal (%)	24.2%	31.1%	23.5%	0.19	21.1%	24.2%	0.38
Peri-menopausal (%)	6.4%	4.1%	6.7%		0.0%	6.6%	
Post-menopausal (%)	63.9%	63.5%	64.0%		78.9%	63.6%	
Unknown (%)	5.5%	1.4%	5.8%		0.0%	5.6%	
Anthropometrics							
Mean Weight in lbs	177.6	184.1	177.0	0.21	185.7	177.4	0.55
Mean Height in ft'in"	5'5"	5'3"	5'5"	0.68	5'3"	5'5"	0.77
Race/Ethnicity							
Caucasian(%)	34.6%	27.0%	35.3%	0.54	15.8%	35.0%	0.43
African American(%)	55.0%	62.2%	54.3%		73.7%	54.7%	
Hispanic(%)	1.3%	1.4%	1.3%		0.0%	1.3%	
Other(%)	8.1%	9.5%	8.0%		10.5%	8.0%	
Not Mentioned(%)	1.0%	0.0%	1.1%		0.0%	1.0%	

Standard IBC = (ICD-O 8530 or EOD-E 710-730 or AJCC T4d), Clinical IBC = Any two signs of erythema, edema, peau d'orange or peau d'orange alone.

P-values for differences between IBC and non-IBC for both criteria based on Chi-square Test (or Fisher's test for cell counts <5) for categorical variables and t-tests for continuous variables.
Sample size: Mean age (n=915), Mean tumor size (n=814), Mean weight (n=887), Mean height (n=880).

Table 4.3: Characteristics of all Breast Cancer Cases (n=915) by Categories of IBC Clinical Criteria

Signs	Most Likely IBC	Possible IBC	Not IBC	p
Total Number of Cases (%)	8 (0.9%)	66 (7.2%)	841 (91.9%)	-
Erythema (%)	**8 (100%)**	**27 (40.9%)**	**26 (3.1%)**	**0.00**
Edema (%)	**8 (100%)**	**30 (45.5%)**	**20 (2.4%)**	**0.00**
Peau d'orange (%)	**8 (100%)**	**46 (69.7%)**	**0 (0.0%)**	**0.00**
Angiolymphatic invasion (%)	**2 (25.0%)**	**17 (12.5%)**	**105 (25.8%)**	**0.01**
Ulcerations (%)	**1 (12.5%)**	**10 (15.2%)**	**24 (2.9%)**	**0.00**
Palpable mass (%)	**6 (75.0%)**	**64 (97.0%)**	**758 (90.2%)**	**0.06**
Diffuse enlargement (%)	**5 (62.5%)**	**20 (30.3%)**	**23 (2.7%)**	**0.00**
Bruising (%)	0 (00.0%)	2 (3.0%)	12 (1.4%)	0.56
Warmth (%)	**0 (00.0%)**	**2 (3.0%)**	**0 (0.0%)**	**0.00**
Nipple retraction (%)	**2 (25.0%)**	**13 (19.7%)**	**46 (5.5%)**	**0.00**
Dermal lymphatic invasion (%)	**1 (12.5%)**	**2 (3.0%)**	**12 (1.4%)**	**0.03**

p-value for difference (Chi-square or Fisher's exact test with cell counts<5).
Most Likely IBC= all three main clinical characteristics noted as present (erythema, edema, peau d'orange)
Possible IBC = any two main clinical characteristics or peau d'orange only noted as present
Not IBC = erythema only, edema only, or no clinical characteristics noted as present

Table 4.4: Characteristics of Breast Tumors With and Without Dermal Lymphatic Invasion (DLI)

	DLI (n=15)	No DLI (n=900)	p-value
Mean age (years)	58.1	57.4	0.80
Mean tumor size (cm)	3.9	1.4	**0.003**
Erythema (%)	26.7%	6.3%	**0.014**
Edema (%)	26.7%	6.0%	**0.011**
Peau d'orange (%)	6.7%	6.1%	0.600
Angiolymphatic invasion (%)	60.0%	12.8%	**<0.001**
Ulcerations (%)	33.3%	3.3%	**<0.001**
Palpable mass (%)	86.7%	90.7%	0.420
Diffuse enlargement (%)	6.7%	5.2%	0.560
Bruising (%)	0.0%	1.6%	0.800
Warmth (%)	0.0%	0.2%	0.970
Nipple retraction (%)	6.7%	6.7%	0.650
IBC mentioned (%)	26.7%	3.0%	**0.001**
ER			
ER positive (%)	26.7%	65.4%	**0.004**
ER negative (%)	73.3%	32.4%	
ER missing (%)	0.0%	2.1%	
PR			
PR positive (%)	20%	55.7%	**0.013**
PR negative (%)	80%	42.1%	
PR missing (%)	0%	2.2%	
Her2			
Her2 positive (%)	33.3%	16.7%	0.170
Her2 negative (%)	66.7%	77.8%	
Unknown (%)	0.0%	5.6%	
Menopausal status			
Pre-menopausal (%)	21.4%	24.2%	0.660
Peri-menopausal (%)	14.3%	6.3%	
Post-menopausal (%)	57.1%	64.2%	
Unknown (%)	7.1%	5.2%	
Race/Ethnicity			
Caucasian (%)	50%	34.6%	0.660
African American (%)	50%	55.4%	
Hispanic (%)	0%	1.3%	
Other (%)	0%	8.3%	
Not Mentioned(%)	0%	0.3%	

	DLI (n=15)	No DLI (n=900)	p-value
Anthropometrics			
Mean Weight in lbs	174.0	178.6	0.740
Mean Height in ft'in"	5'4"	5'5"	0.920

P-values for differences between DLI and non-DLI based on Chi-square Test (or Fisher's test for cell counts <5) for categorical variables and t-tests for continuous variables
Sample size: Mean age (n=915), Mean tumor size (n=814), Mean weight (n=888), Mean height (n=880),

Table 4.5: Odds Ratios for Tumor Characteristics Associated with Dermal Lymphatic Invasion (DLI)

	Crude Odds Ratio	95% CI
Angiolymphatic invasion	10.2	(3.6, 29.3)
Ulcerations	14.5	(4.7, 45.0)
ER (negative vs. positive)	5.5	(1.8, 17.6)
PR (negative vs. positive)	5.3	(1.5,18.9)
Erythema	5.4	(1.7, 17.4)
Edema	5.7	(1.8, 18.5)
Mean tumor size	1.2	(1.1, 1.3)

Sample Size for Angiolymphatic invasion, Ulcerations, ER, PR, Erythema, and Edema: DLI (n=15,) no DLI (n =900),
Sample Size for Mean tumor size: DLI (n=13), no DLI (n=801)

Table 4.6: SEER Coding for the Discrepant IBC Cases and Neoadjuvant IBC cases

SEER code	Text	Discrepant IBC (n=59) #	%	Neoadjuvant IBC (n=50) #	%
CS_EXT					
100	Confined to breast, localized	34	57.6%	14	28.0%
190	T2, NOS	1	1.7%	1	2.0%
200	Local skin infiltration	1	1.7%	1	2.0%
300	Invasion muscles	4	6.8%	4	8.0%
400	Chest wall invasion	4	6.8%	4	8.0%
510	T4b (clinical signs <50%)	10	16.9%	8	16.0%
520	T4b (clinical signs >50%)	4	6.8%	4	8.0%
610	T4c	1	1.7%	1	2.0%
710	IBC without clinical >50% (T4b)	0	0.0%	7	14.0%
725	IBC with clinical >.33% but <50%	0	0.0%	1	2.0%
730	IBC with clinical signs >50% (T4d)	0	0.0%	5	10.0%
Histology ICDO3					
8010	Carcinoma, NOS	0	0.0%	1	2.0%
8140	Adenocarcinoma	2	3.4%	3	6.0%
8490	Signet Ring Cell Adenocarcinoma	0	0.0%	1	2.0%
8500	Ductal	42	71.2%	34	68.0%
8507	Intraductal micropapillary carcinoma	1	1.7%	2	4.0%
8520	Lobular	4	6.8%	2	4.0%
8522	Mixed Ductal and Lobular	5	8.5%	4	8.0%
8523	Infiltrating Ductal with other	2	3.4%	2	4.0%
8575	Metaplastic, NOS	2	3.4%	1	2.0%
8980	Carcinosarcoma, NOS	1	1.7%	0	0.0%
Derived AJCC6 T					
15	T1b	2	3.4%	0	0.0%
18	T1c	11	18.6%	4	8.0%
20	T2	16	27.1%	9	18.0%
30	T3	10	16.9%	7	14.0%
41	T4a	4	6.8%	4	8.0%
42	T4b	14	23.7%	12	24.0%
43	T4c	1	1.7%	1	2.0%
44	T4d	0	0.0%	13	26.0%
88	n/a	1	1.7%	0	0.0%

CS_Ext =SEER collaborative staging extension codes
Discrepant IBC = Cases determined to be IBC by the main clinical criteria but not coded as IBC in SEER
Neoadjuvant IBC = Cases determined to be IBC by the main clinical criteria and also received neoadjuvant chemotherapy

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Chapter 5

Conclusion

5.1: Summary of Findings

Globally, the occurrence of breast cancer is distributed heterogeneously, with incidence being higher in many areas of the developed world as compared to developing countries [1]. This dissertation focused on understanding the trends in breast cancer and specifically evaluating inflammatory breast cancer occurrence from a global perspective. We described trends in breast cancer occurrence by age, stage at diagnosis, and hormonal status in the Gharbiah population-based cancer registry in Egypt. This study adds to our understanding of breast cancer in this region, which is at an important stage of demographic and health transition. Furthermore, we evaluated the occurrence of inflammatory breast cancer (IBC) among Arab American women in the Detroit, California, and New Jersey Surveillance, Epidemiology and End Results (SEER) registries. As IBC has been reported to be more common in many areas of the Arab world [2,3], this study was critical to our overall understanding of IBC occurrence among Arab Americans and other racial and ethnic populations in the United States. Finally, we assessed the lack of standardization in IBC diagnosis and registration across regions by comparing differing criteria to identify IBC cases from medical records and the SEER

registry. The criteria utilized to identify and classify IBC cases greatly impacts the estimated measures of occurrence, and the differing criteria must be considered when interpreting and designing any epidemiologic study of IBC. An overall summary of our findings for each study in this dissertation is included in the following section.

Chapter 2 examined the trends in breast cancer incidence by age, hormonal receptor status and stage of diagnosis in Egypt from 1999-2008 and made projections for breast cancer occurrence for the years 2009-2015. Our analysis demonstrated a considerable increase in breast cancer incidence rates in this region from 1999-2008, particularly among women 50 years and older. However, due to population changes, we found that the greatest expected increase in breast cancer caseloads from 2009-2015 is among women aged 30-49 years. Furthermore, our study noted a general decline in the incidence of distant tumors in Gharbiah, Egypt from 1999-2008, and a potential increase in the incidence of estrogen receptor (ER) negative tumors. These results have important implications for allocating limited resources, managing treatment needs, and exploring the consequences of prior interventions and/or changing risk factors in Egypt and other developing countries at the same stages of demographic and health transitions.

In Chapter 3, we evaluated differences in the proportion of IBC out of all breast cancers and IBC characteristics by race/ethnicity, including among Arab American women. This study demonstrated significant differences in the presentation of IBC and the proportion of IBC out of all breast cancers by racial/ethnic group. Our results suggest significant differences in IBC occurrence by ethnicity after accounting for differences in

age, hormonal receptor status, registry, and census-tract level educational status. Women who were Arab American, Non-Hispanic Black, American Indian/Alaskan natives, and Hispanics all had increased odds of IBC as compared to Non-Hispanic White women. Asian women had a decreased odds of IBC compared to Non-Hispanic White women. Furthermore, we found that American Indian/Alaskan natives, Hispanics and Non-Hispanic Blacks had shorter mean survival time after IBC diagnosis as compared to Non-Hispanic Whites, Arab Americans and Asian women. With the significant lack of epidemiologic data on IBC, this study represents important progress to our understanding of this aggressive disease.

As part of Chapter 4, we explored the lack of standardization in the diagnosis of IBC. This study evaluated global differences in IBC and applied an identical case ascertainment system used in North Africa to medical records in the United States in order to provide evidence to support or refute the claim that IBC is more common in North Africa. We compared diagnostic factors of IBC reported in a SEER registry to clinical criteria found in the medical records of all invasive breast cancer cases at a single institution. Further, we estimated the proportion of IBC out of all breast cancers using clinical criteria to define IBC cases from medical records. To our knowledge, this is the first study to utilize the precise IBC clinical criteria used in our previous work in Egypt to calculate the proportion of IBC out of all breast cancers at a cancer center in the United States, for the purpose of improving our understanding of global variation in the occurrence of IBC. Utilizing only the clinical criteria at a comprehensive cancer center in Detroit, Michigan from 2007-2009, we found that 8.1% of breast cancers were IBC. It

has previously been reported that between 1% and 6% of all patients with breast cancer in the United States have IBC [4-6]. These results suggest for the first time, that the incidence of IBC is likely to be significantly underestimated in the US. Furthermore, in our study sample we found significant differences in tumor characteristics between IBC cases with and without dermal lymphatic invasion of tumor emboli (DLI), suggesting potential etiologic subtypes of IBC based on the presence of DLI. This study highlights the lack of standardization in defining IBC and emphasizes the importance of understanding these limitations when comparing results across studies. The findings of this study add to our understanding of the global variation in IBC incidence and have important implications for diagnosis, treatment, prognosis and future research on IBC. Therefore, emphasis must be placed on the documentation of clinical and pathological characteristics of IBC in the medical record, so that analysis of putative IBC subtypes will be possible and we can further evaluate and come to a consensus on the definition of IBC to be utilized in future research.

In summary, our findings demonstrate significant increases in breast cancer incidence in an area of the world at a pivotal point of transition. While there does appear to be some improvement in the downstaging of breast cancer diagnosis in this region, we still observed a much higher percentage of breast cases being diagnosed at regional and distant stages as compared to what is seen in the United States. Furthermore, the increase in ER negative tumors in Egypt is unlike what has been observed in the United States. These results may have implications for other regions of the world at similar stages of economic progress. Our findings can also be used to implement meaningful

recommendations for cancer control and planning in a region with limited resources. Moreover, this research highlights important differences by racial and ethnic groupings in the occurrence of IBC in the SEER registries. Understanding the racial disparities in IBC occurrence can generate hypotheses about potentially modifiable risk factors for this aggressive disease. Finally, this dissertation provides provocative evidence of the lack of standardization in IBC diagnosis and registration over time and place. This finding is critical for interpreting epidemiologic research on IBC and can be used as an impetus to work toward a consensus for a ubiquitous definition for IBC diagnosis and registration.

5.2: Strengths and Limitations

Strengths of this dissertation include our global approach to characterizing the trends and heterogeneity of breast cancer occurrence across regions with varying levels of risk factors. This research is essential for understanding the etiology of breast cancer and hypothesizing potentially modifiable risk factors. Understanding breast cancer from a global perspective is paramount given the rapidly increasing burden of cancer in many areas of the developing world, where there is often limited capacity to detect and treat cancers.

Our study of breast cancer trends in Egypt has numerous strengths, including the use of a well-characterized and validated population-based registry data from a 10-year period. The study also provides predictions for future trends, which are critical for cancer control and planning efforts in Egypt. Finally, we identified important information on the progress of downstaging efforts in Egypt, as well as trends in hormonal receptor status of

tumors, which are critical for cancer treatment planning, especially in developing countries with limited treatment resources.

Our study of IBC occurrence among Arab Americans included the use of large-scale population-based SEER registry data, which is considered to be reliable and accurate as it meets International Agency for Research on Cancer (IARC) standards, ensuring a certain degree of data quality and comparability based on a number of factors [7]. Further, the IBC case ascertainment definition used in the study is considered valid and is not as conservative as previous studies requiring the pathological diagnosis of IBC. The Arab naming algorithm to identify Arab ancestry has been constructed and utilized in previous studies to describe relative proportion of cancer among this population [8-10]. Finally, this study was innovative as it maximized the number of Arab Americans represented in the study sample by including data from California, Detroit, and New Jersey registries, where the expected number of Arab Americans is expected to be maximized.

Finally, our medical record review of IBC diagnosis is the first study to our knowledge to utilize the precise IBC clinical criteria used in previous work in Egypt to calculate the proportion of IBC out of all breast cancers at a cancer center in the United States, for the purpose of improving our understanding of global variation in the occurrence of IBC. This study design allowed us to use an identical system to ascertain IBC cases in global comparative analyses. A further strength of this study is that it highlights the lack of standardization in defining IBC and stresses the importance of understanding these limitations when comparing results across studies.

This dissertation does have several important limitations. In our analysis of breast cancer trends in the Gharbiah population-based registry, the stage at diagnosis and hormonal receptor status information was missing for a large proportion of the cases. Furthermore, the persistence of unknown stage and hormonal receptor status throughout the study years is disconcerting. We found statistically significant differences in the percentage of missing stage data across age groups and regions contributing cancer cases to the Gharbiah registry. Additionally, ER and progesterone receptor (PR) information was more likely to be missing among women aged 70+ and among distant tumors. This missing information may have limited our ability to demonstrate a significant measure of trend and could produce bias in our estimates of the trends in breast cancer occurrence in Egypt. A further limitation is the fact that the breast cancer projections reported in this study assume stable screening practices, risk factor profiles and constant incidence rates from 2008. Future predictions are affected by population growth and by aging and changing risk factors, which may be difficult to predict. Thus, while the projections reported in our study are based on statistical models, they should be interpreted with some caution. The further from 2008 the predicted caseloads are, the more prone to error the estimates will be. Moreover, the population figures for the intra-census years were determined using linear interpolation, which assumes constant growth over these years. The accuracy of the calculated incidence rates would be affected if the actual population growth differ from our predicted values. Additionally, registry-specific statistics are based on small numbers of cases per year observed in young women, with an inevitable high degree of variability. Finally, because the possibility of increased detection and improved quality of data collection and classification are difficult to differentiate, the

interpretation of the increased incidence of breast cancer is not straightforward [11]. While advances in diagnostic technology may have had some effect on the apparent increasing incidence of breast cancer over the study period, screening is not widespread in Egypt. Therefore it is unlikely that increased detection of breast cancer accounts for the observed increasing trends in breast cancer incidence in Egypt.

Limitations of our study of IBC occurrence in Chapter 3 include a potential for misclassification of Arab women, especially where the maiden name was unavailable. However, we believe that the possibility of misclassification is limited as many Arab-ancestry women keep their maiden names upon marriage [12-14]; additionally, maiden names are available for a large proportion of the women. Another possible limitation of this study was the lack of information on country of origin or date of immigration to the United States. The Arab American immigrant group is composed of individuals from many diverse Arab nations. Without information on country of origin, we may be missing critical information that could explain disparities in IBC occurrence. Furthermore, we would surmise that immigrants arriving earlier in life would be more likely to experience cancer rates comparable to non-Arab Whites versus immigrants who arrived later [15]. Without information on time of immigration, we may be mixing the effect of IBC occurrence between recent Arab immigrants, who maintain certain cultural norms from their countries of origin, with Arab women who have become acculturated to the Western lifestyle, being born in or having lived in the U.S. for a considerable amount of time. It would be beneficial to evaluate IBC cancer occurrence by time of immigration

among migrant groups in the U.S. in order to understand potential environmental risk factors for the disease.

Additionally, while SEER data is considered to be of superior quality, it has been suggested that under ascertainment of cancer cases in SEER was more common among younger patients, non-white minorities, and lower income groups [16]. However, we do not believe that this will be a significant concern for our study as the SEER registries have been utilized in many studies investigating racial/ethnic disparities in cancer. A further limitation could be the use of different laboratories to determine hormonal receptor status in our dataset. Moreover, the hormonal receptor data were not routinely collected during our study period, so we do have to be concerned about missing data for these variables. To overcome this limitation, we restricted our analysis on ER/PR from 1990 forward and on Her2 from 1999 forward, when this information was more regularly reported in the SEER registries. Furthermore, the lack of data on other potentially important covariates including reproductive factors, obesity, individual-level SES, and urban/rural status could lead to residual confounding in our analysis. It is also important to consider that our data came from the Detroit SEER, which only includes 3 counties in Michigan, while the California and New Jersey registries are state-wide. This could potentially affect the generalizability of our results if we think that these registries are not representative of the overall population of women with breast cancer in the United States. In addition, our study was limited in calculating the proportion of IBC out of all breast cancer instead of IBC incidence rates to evaluate racial disparities. If denominator data were available for the Arab population in the SEER geographic areas, we would have been able to calculate age-standardized incidence rates for the racial groups. Finally, this

is a purely descriptive analysis, and we are unable to draw causal inferences from the study findings.

Limitations of the medical record review study in Chapter 4 include the use of hospital medical records and not a population-based sample. Women who received care at the cancer center were more likely to have aggressive disease, with more serious prognoses and therefore would have been more readily referred to a tertiary facility; for all these reasons, this hospital-based group would be predicted to exhibit higher stage at diagnosis when compared to the rest of the metropolitan Detroit area (data not shown). Thus, while we found the proportion of IBC out of all breast cancers to be higher at this comprehensive cancer center, this may not be true in a US population-based sample. Further, our ability to apply this clinical criterion for IBC case identification is predicated on the quality of medical records. If the quality of medical records varies significantly between countries, we will still be limited in our ability to draw conclusions on global differences in IBC occurrence. However, hospital medical records are typically considered accurate and adequate for use in epidemiologic research of this kind, and the clinical diagnostic criteria used in this study have been successfully applied to medical records in a previous study [3]

5.3: Public Health Impact and Future Directions

The main findings of this dissertation have significant implications for our overall understanding of breast cancer etiology and disparities in IBC occurrence. Our analysis

of breast cancer trends in the Gharbiah population-based cancer registry in Egypt provides critical information to inform clinicians and policy makers in Egypt. Having detailed information on what to expect in terms of breast cancer trends by stage and hormonal receptor status can help address disparities in the presentation of disease by focusing early detection efforts on vulnerable populations. Furthermore, this analysis aids in our understanding of the etiology of the breast cancer in a setting that differs in regard to its risk factor profile as compared to many developed countries. Understanding the temporal trends in breast cancer can facilitate cancer control and treatment planning efforts, which are particularly critical in settings with limited resources. Our finding of an increase in ER negative tumors over the study period, especially among older women warrants future research. Finally, we strongly believe that emphasis must be placed on supporting cancer registries around the globe; without accurate data, we cannot conduct comparative analyses to understand the etiology of cancer and plan cancer control strategies.

By evaluating racial disparities in IBC occurrence, we hope to generate further hypotheses about potentially modifiable risk factors for IBC. With the significant lack of epidemiologic data on IBC, this study represents important progress to our understanding of this aggressive disease. Future research should focus on etiologic factors that may underlie the racial/ethnic differences in IBC occurrence, and also examine country of origin and date of immigration to the U.S. to further elucidate potentially modifiable risk factors for IBC. Finally, American Indian/Alaskan natives were found to have the shortest mean survival time after IBC diagnosis in our study, and efforts to reach these populations for early treatment of disease should become a priority.

Our study of differing criteria to identify IBC cases from medical records and registries has significant implications on future epidemiologic research on IBC. Findings from this study highlight the importance of standardizing the diagnostic criteria in IBC and understanding the coding changes implemented in SEER around IBC. Furthermore, emphasis must be placed on the documentation of clinical and pathological characteristics of IBC in the medical record, so that analysis of putative IBC subtypes will be possible and we can further evaluate and come to a consensus on the definition of IBC to be utilized in future research. The findings of this study add to our understanding of the global variation in IBC incidence and have important implications for diagnosis, treatment, prognosis, and future research on IBC.

5.4: Conclusion

Cancer incidence is rising around the world due to population growth, aging, the impact of changes in behavioral risk factors, and reduced mortality from infectious diseases [17]. The developing world may be ill-prepared to deal with the consequences of an increase in cancer diagnoses both financially and socially. The lack of infrastructure and financial assets may lead to additional suffering associated with a cancer diagnosis, some of which could be avoided with increased resources. Therefore, breast cancer in the developing world is a growing public health concern and significant efforts should be afforded to address this increasing burden.

Overall, this dissertation contributes to a better understanding of global heterogeneity in breast cancer and IBC. The observed trends in breast cancer in Egypt add to our overall understanding of the etiology of this disease and can be used to inform

clinicians and policy makers in order to prioritize resources to detect and treat cancer in this region of the world. Furthermore, by describing IBC occurrence in Arab Americans in the United States, we hope to generate further hypothesis about potentially modifiable risk factors for IBC. With the significant lack of epidemiologic data on IBC, this study represents important progress to our understanding of this disease. Finally, our study results demonstrate for the first time that IBC may be underestimated in the United States SEER registries. Therefore, special attention must be afforded to the intricate coding changes affecting the identifiability of IBC from the SEER registries over time. Overall, this research represents progress toward research on chronic diseases in the developing world and draws attention to the importance of IBC, which may lead to increased funding and support toward this rare disease. In summary, this research contributes concrete scientific evidence to our understanding of breast cancer and specifically IBC, which will help reduce the global burden of this disease.

5.5: References

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Appendix 1

Equations from Chapter 2

AAPC is derived by first estimating the underlying joinpoint model that best fits the data. We specified the joinpoint parameters based on rate data for the incidence rate trends and counts for the estimation of future caseloads. The AAPC over the fixed interval of time is a weighted average of the slope coefficients of the underlying joinpoint regression line with the weights equal to length of each segment over the time interval (number of years the APC segment contributes to the AAPC denominator). The final step of the calculation transforms the weighted average of slope coefficients to an annual percent change.

If we denote b_1s as the slope coefficients for each segment in the desired range of years, and the w_1s as the length of each segment in the range of years, then:

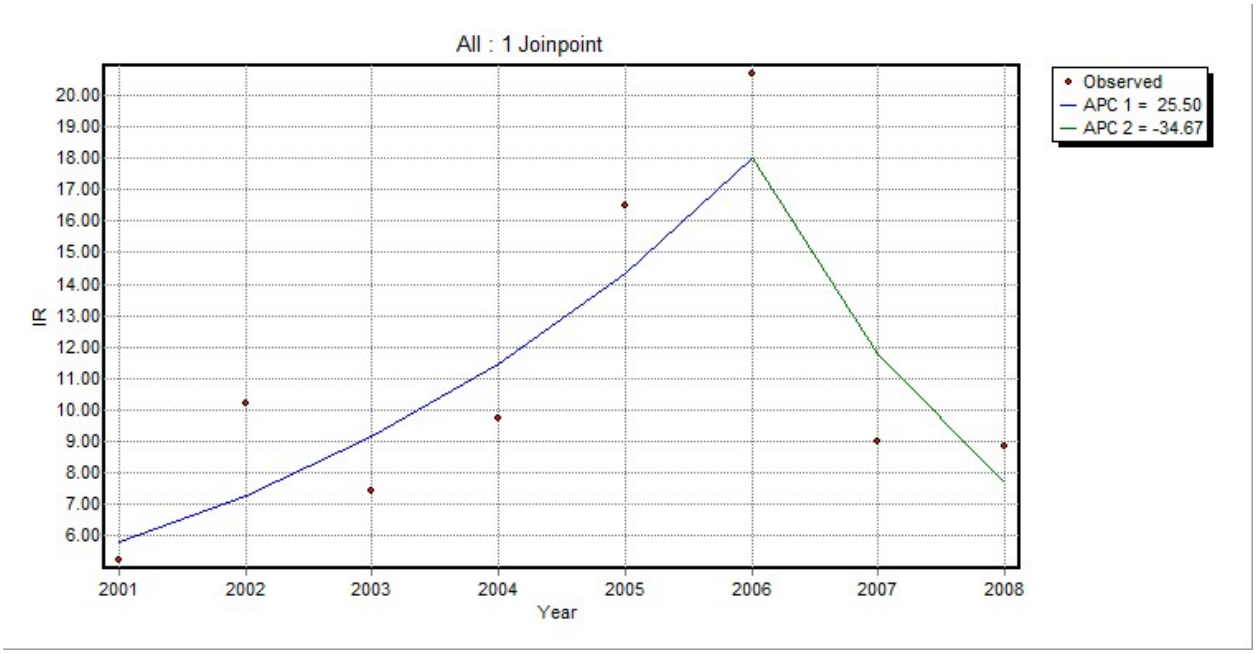
$APC_i = \{Exp(b_1)-1\} \times 100$

and

$AAPC = \{Exp (\sum w_i b_1 / \sum w_i) -1\} \times 100$

*where no joinpoints are determined, the AAPC = APC

Example:



Joinpoint 1 =2006

Segment 1: APC=25.50 (slope=0.227111) and weight = 5 (5 years: 2001-2006)

Segment 2: APC=-34.67 (slope=-0.425695) and weight =2 (2 years: 2006-2008)

AAPC from 2001-2006 $=\{\text{Exp}\ (\sum w_i b_1 / \sum w_i) - 1\} \times 100$

$=\{\text{Exp}\ ((5*0.227) + (2*-0.426))/(5+2) - 1\} * 100$

$= \text{Exp}\ \{((1.135 + -0.852) / 7) - 1\} * 100$

$= -9.5$

Appendix 2

Equations from Chapter 3

We used hierarchical logistic regression models (HLM) in SAS Glimmix procedure (version 9,1; SAS Institute Inc) to model the association of race and inflammatory breast cancer accounting for individual-level and census-tract level variables.. This model accounts for the hierarchical structure and clustering of the data by specifying random effects for the individual-level and census tract-level variables. For example, women who live within the same census tract may be more similar in regard to unmeasured characteristics as compared to individual women across different census-tracts. Therefore, a hierarchical modeling structure allows for the examination of both individual- and census tract-level effects while accounting for the effect due to clustering within census-tracts through the addition of a random intercept, leading to more accurate standard error estimates.

We modeled the association between race and IBC among all women with breast cancer using hierarchical logistic regression models, adjusting for age, tumor marker status, registry and a census tract-level education variable. Confounders were included in the model based upon our prior knowledge and change-in-estimate criteria between the crude and adjusted measures. We tested for interactions between race and each of the characteristics; significant interactions were retained in the model along with their main effects.

The final HLM model for log odds of IBC in our study is detailed below:

$$\text{logit}(\pi_{ij}) = \alpha + \Upsilon(\text{Education})_j + \mu_j + \beta_1(\text{Race})_{ij} + \beta_2(\text{Age})_{ij} + \beta_3(\text{ER})_{ij} + \beta_4(\text{PR})_{ij} + \beta_5(\text{Her2})_{ij} + \beta_6(\text{registry})_{ij} + \beta_7(\text{Race*ER})_{ij}$$

where: α = census-tract level intercept

Υ =census-tract level education fixed effect

μ_j = census-tract level random effects

β_1 = individual fixed effect for Race

β_2 = individual fixed effect for Age

β_3 = individual fixed effect for estrogen receptor status (ER)

β_4 = individual fixed effect for progesterone receptor status (PR)

β_5 = individual fixed effect for human epidermal growth receptor 2 status (Her2)

β_6 = individual fixed effect for Registry

β_7 = product term for interaction of Race by ER status

Appendix 3

Equations from Chapter 4

McNemar's Test for correlated proportions: non-parametric test accounting for the correlated nature of our sample by determining whether the marginal proportions differed between groups (SEER vs. clinical criteria for IBC). It is applied to a 2x2 contingency table with matched pairs, to determine whether the row and column marginal frequencies are equal ("marginal homogeneity").

	SEER IBC	SEER non-IBC	Row total
Clinical IBC	A=15	B=59	A+B=74
Clinical non-IBC	C=4	D=837	C+D=841
Column total	A+C=19	B+D=896	N=915

H_o=probability (A) + probability (B) = probability (A) + probability (C) and probability (C) + probability (D) = probability (B) + probability(D)

or $p_b=p_c$

$H_A= p_b \neq p_c$

The McNemar test statistic is:

$\chi^2 = (b-c)^2 /b+c = (59-4)^2/59+4 = 48.02$, looking at chi square distribution table, with 1 df, this is statistically significant at the alpha 0.05 level.

Further, we utilized logistic regression models to assess tumor characteristics associated with pathological evidence of disease (DLI). These models are detailed below:

$\text{logit pr (DLI)} = \beta_0 + \beta_1 X$

where β_0 = baseline risk or log odds for DLI in study sample

β_1= log odds (DLI) for each tumor characteristic (X)

X = angiolymphatic invasion, ulcerations, ER (negative vs. positive), PR (negative vs. positive), erythema, edema, mean tumor size
*in subsequent models

$\exp(\beta_1)$ = crude odds ratio for DLI by each value of X