

**Variation in Inflammatory and Early Onset Breast Cancer Incidence and Survival
by Geography, Socioeconomic Position, and Tumor Characteristics**

by

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To my mother, Kathy, who was diagnosed with breast cancer seven years ago. Her diagnosis and subsequent treatment have inspired me to research the causes of breast cancer so one day other women can be spared the physical and emotional consequences of this disease.

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Abstract

Inflammatory and young-onset breast cancers are relatively rare and have a poor prognosis. The first two projects of this dissertation utilize the United States (US) Surveillance, Epidemiology, and End Results (SEER) database to examine inflammatory breast cancer (IBC) incidence and survival by county level socioeconomic position (SEP) in order to help elucidate potential risk and prognostic factors for this aggressive form of breast cancer. A number of studies have suggested a young-onset, rapidly progressing form of breast cancer may be more common in North Africa. However, little research exists examining the characteristics of breast cancer in this region. The third project of this dissertation is an age-stratified comparison of breast cancer characteristics between Egypt and the US using the Gharbiah, Egypt population based cancer registry (GCR) and the US SEER database.

While overall breast cancer has been found to be positively associated with SEP, in this dissertation's first project, IBC was associated with decreasing county-level SEP. Incidence rates for IBC generally increased as SEP decreased, while the opposite was found for non-IBC. Hierarchical logistic regression models showed Black, American Indian/Alaska Native, Hispanic White race/ethnicity, low county-level SEP, and younger age are associated with higher odds of IBC, in decreasing order of the size of the effect.

In this dissertation's second project, the Kaplan-Meier survival analysis showed that IBC has worse survival than non-IBC. Residing in a lower SEP, rural county significantly lowers survival for non-IBC in multivariate proportional hazards models.

Subjects of Black race/ethnicity appear to have worse survival regardless of BC type, stage, county-level SEP, tumor, or treatment characteristics.

This dissertation's third project identified significant in age at diagnosis, tumor grade, hormone receptor status, histology, and stage differences between Egyptian and US breast cancer cases. These differences persisted in age-stratified and multivariate analysis. Egyptian cases were on average younger and were more likely to have tumors that were hormone receptor negative, ductal histology, and diagnosed at higher stage in multivariate models, though the majority of Egyptian tumors were grade II. These differences in tumor and patient characteristics held in age-stratified analysis. The finding that Egyptian cases were more likely to be diagnosed at later stages even after adjustment for age, hormone receptor status, histology, and grade indicates there is likely opportunity to intervene earlier in the disease process.

This dissertation contributes to the literature on the multi-faceted relationship between SEP, race, geography, and other individual and ecologic factors associated with IBC and young-onset breast cancer incidence and survival, as well as in identifying groups that are more likely to be diagnosed with and have worse survival from these aggressive breast cancers, although the categories are broad. This will aid in directing screening and treatment to currently underserved populations that will likely benefit the most from these programs.

Chapter 1

Introduction

Overview

Breast cancer (BC) is the most commonly diagnosed cancer among women in the United States (US) (excluding skin cancer) and worldwide (1, 2). The International Agency for Research on Cancer estimated approximately 1.38 million women worldwide were newly diagnosed with BC in 2008, with the American Cancer Society estimating 207,090 new cases of invasive BC in the US in 2010 (1, 2). BC is the second leading cause of cancer death in US women behind lung cancer, with an estimated 39,840 deaths attributed to BC in 2010 (1). Worldwide, BC is the leading cause of cancer death among women, with an estimated 458,000 BC deaths in 2008 (2).

BC is a heterogeneous disease, with incidence and survival dependent on many factors. These factors include clinical and pathologic features such as age at diagnosis; and sociodemographic factors such as race/ethnicity and country of residence (3). Inflammatory and young-onset BC are two sub-types of BC that are relatively rare and carry a very poor prognosis (4-8). Due in part to its rarity and lack of standard case definition, there have been few analytic epidemiologic studies examining risk factors for inflammatory breast cancer (IBC), and little is known regarding IBC's association with socioeconomic position (SEP) (4, 5). Therefore, the first two projects in this dissertation utilize the US Surveillance, Epidemiology, and End Results (SEER) database to examine

IBC incidence and survival by census derived county level SEP variables in order to help elucidate potential risk and prognostic factors for this rare and deadly form of BC.

Several population based studies in the US have pointed to differences between young- and late-onset BC suggestive of different etiologies (9-20). Numerous non-population based studies conducted in the North African country of Tunisia have suggested a young-onset, rapidly progressing form of BC may be more common in this region (21-25). However, no population based studies specifically examining the characteristics of young- vs. late-onset BC in a North African country as compared to the US have been conducted. Therefore, the third project of this dissertation is an inter-country comparison of Egypt and the US using data from the population based cancer registry of the Gharbiah region in Egypt and the US SEER database.

Inflammatory Breast Cancer Incidence

The diagnosis of IBC is primarily a clinical one. The American Joint Committee on Cancer's (AJCC) definition, the most widely used, describes IBC typically presenting with diffuse erythema, edema, and peau d'orange over a third or more of the skin of the breast. According to the AJCC staging scheme, IBC tumors are given the T4d designation, and are staged at IIIB or above depending on nodal and/or distant metastases (26). Although IBC can be of various histologic types, it is most commonly seen as infiltrating ductal carcinoma (27, 28). As the diagnosis of IBC relies on subjective judgment of clinical symptoms and history taking about the symptom duration and evolution, misdiagnosis and ultimately misclassification in tumor registries are rather common compared to other forms of BC. This hampers not only research of incident

IBC, but also treatment for patients, the early receipt of which is critical due to the aggressive nature of IBC (29).

At the beginning of the SEER program in 1973, IBC was coded according to the International Classification of Diseases for Oncology (ICD-O) 8530 designation. ICD-O code 8530 is a pathologic designation requiring plugging of the dermal lymphatics with tumor emboli and does not consider clinical skin changes (4). However, this conservative IBC definition is not consistent with the current AJCC staging manual guidelines, and likely underestimates the true incidence of IBC (4, 30-32). More recent SEER based IBC studies have used a combination of the ICD-O 8530 code along with SEER Extent of Disease (EOD) codes in order to ensure more complete IBC case capture (4, 33-35). SEER EOD codes are based on a combined clinical and operative/pathologic assessment abstracted from the pathology report, and allow for identification of IBC cases that do not have ICD-O 8530 as the pathologic diagnosis (30).

A number of studies have examined IBC incidence using the US SEER and North American Association of Central Cancer Registries databases, although comparisons across these studies is difficult due to differing IBC case definitions used and time periods studied (4, 9, 11, 13, 14, 30, 31, 33, 34, 36, 37). Estimates for the overall incidence rate of IBC generally range from 0.9 per 100,000 woman-years using only ICD-O code 8530 up to 2-3 cases per 100,000 woman-years when using a comprehensive case definition, with the total percentage of IBC cases out of all BC ranging from approximately 1-2% depending on case definition used (4, 14, 31, 34).

IBC tends to be diagnosed at younger ages than other BC types, with US studies generally reporting median/average age at diagnosis of approximately 56-58 years, as

compared to approximately 61-62 years of age for BC overall (4, 11, 13, 30, 31, 33, 34). Incidence and age at IBC diagnosis also vary by race/ethnicity. In the US, African Americans have a higher incidence rate of IBC as compared to white women, and also tend to be diagnosed at younger ages (4, 11, 30, 31, 34, 37). Although little data exists regarding IBC incidence in other US racial/ethnic groups, it appears Asian/Pacific Islander women have the lowest incidence of IBC in the US, with no difference in incidence seen between Hispanic and non-Hispanic women (31, 37). Furthermore, it has been reported that American Indian/Alaska Native women have the lowest median age of IBC onset (49.5 years), followed by African American and Asian/Pacific Islander women (54 years), with White women having the oldest median age of onset at 58 years (4).

Although in the US it is well documented that overall BC incidence is positively associated with SEP and urban residence, little is known regarding the association of SEP and area of residence with the incidence of BC subtypes, including IBC (38-49). Given the lack of knowledge about factors associated with IBC incidence, especially with regard to SEP and area of residence, the first study contained in this dissertation, published in the journal *Cancer Epidemiology, Biomarkers & Prevention*, examines the association of county-level SEP measures to IBC and non-IBC incidence in the US SEER database linked to 2000 US Census county-attribute data for the years 2000-2007 (50).

Inflammatory Breast Cancer Survival

Most survival information on IBC, both in the US and internationally, comes from small scale, single institution studies. It is difficult to draw conclusions based on these studies due to treatment differences across institutions at different time periods and

variation in case definitions, but in general these smaller studies have consistently reported IBC carries a poor prognosis, more so than other forms of BC including non-IBC locally advanced BC (LABC) (21, 51-58). As in other types of BC, estrogen receptor positive (ERP) IBC carries a better prognosis (58), though Human Epidermal Growth Factor Receptor 2 (HER2/neu) over-expression's role in IBC prognosis remains unclear as it does not appear to be an important independent predictor of outcome as in non-IBC (59, 60).

Examining IBC survival among patients enrolled in clinical trials allows for nearly complete control of treatment differences as ideally all patients within a particular treatment arm will receive identical therapy. Unfortunately, there have been no large scale, multi-institutional clinical trials examining the optimal chemotherapeutic regimen for IBC patients (29). In an early single-arm, phase II prospective non-randomized trial of 89 patients receiving neoadjuvant chemo-hormonal therapy and breast conservation in LABC, including IBC (n=36), Merajver et al. reported inflammatory status was significantly associated with decreased overall survival ($p = 0.037$) and 5-year disease-free survival (IBC 35% vs. non-IBC 50%, $p = 0.020$) (61).

More recent trials have also reported worse overall and progression/event free survival for IBC patients compared to other LABC (62, 63). Therasse et al. reported 5-year survival of 44% for IBC participants in their phase III randomized trial conducted in 12 European countries comparing a standard anthracycline-based regimen to a dose-intensified anthracycline regimen, as compared to 59% in non-IBC LABC participants. IBC participants were also more likely to experience disease progression (Hazard ratio = 1.47, 95% CI: 1.13 to 1.92) (62). Low et al. reported long term results for non-IBC

LABC and IBC patients treated at the National Cancer Institute between 1980 and 1988 in a trial examining multimodality therapy, and found IBC participants had shorter median event-free (3.8 vs. 12.2 years) and overall survival (2.3 vs. 9.0 years) than non-IBC participants (63). Although not as generalizable as large scale population based studies, trials such as these that report estimated survival separately for participants with IBC add valuable information to the IBC literature. These trials allow survival comparisons of IBC to non-IBC LABC cases in a situation where treatment is theoretically the same or very similar, within treatment arms, which is usually not possible in larger population-based survival studies, and thus add further evidence that IBC is a distinct clinical entity with worse prognosis.

Eight population-based studies of IBC survival were reviewed (4, 30, 33, 34, 36, 60, 64, 65). Six (4, 30, 33, 34, 36, 64) of these studies used SEER data, while the other two used US state registries (60, 65). These studies have generally found survival for IBC is lower than non-IBC of comparable stage, and that similar to other BC types, African American race/ethnicity and estrogen receptor negative (ERN) tumors carry the poorest prognosis (30, 34, 60). In one recent IBC survival analyses using SEER data, Hance et al. found the shortest median IBC survival among cases who were African American and ERN (both 2 years), while White (3 years) and ERP cases (4 years) had the longest median survival (34). Several studies have also reported increasing survival time for IBC cases in recent years as compared to previous IBC survival estimates (30, 64), as more intensive therapies are administered and as increased awareness appears to be leading to more prompt recognition of this aggressive breast cancer type (29, 66-71).

Only one population based study has examined SEP in relation to IBC survival. Yang et al. examined IBC outcomes among cases diagnosed from 1988 to 2002 identified from the Florida cancer registry database. The authors reported an overall median survival time of 32 months. Patients residing in affluent areas (poverty <5%) and those with private insurance experienced longer median survival times. In this cohort, all therapies were associated with longer median survival, with chemotherapy before surgery plus receipt of radiation conferring the longest median survival among the different treatment combinations (45.17 months). However, limitations of this study include lack of information on hormone receptor status, an important prognostic factor, as well as only including cases from Florida, which may not be representative of IBC cases in the greater US (65).

The second study in this dissertation, published in the journal *Breast Cancer Research and Treatment*, examines the association of SEP with stage III and IV IBC and non-IBC survival for cases diagnoses between 1990 and 2008 in the US SEER database linked to 1990 and 2000 US Census county-attribute data (72). As this analysis examines county-level SEP while adjusting for important prognostic tumor and treatment characteristics, including hormone receptor status, it aids in elucidating causes for the survival difference and has important implications for the targeting of BC education and health care resources.

Breast Cancer in Egypt

Although numerous studies dating back to the late 1970s have examined a “peculiar” IBC-like BC in the North African country of Tunisia that occurs primarily in

younger women, less is known generally about BC in Egypt (21-23, 25). The Anglo-Egyptian Health Agreement Collaborative Study was one of the first modern studies to comprehensively evaluate BC in Egypt, and was designed to compare serum hormone levels and response to endocrine therapy in Egypt and Great Britain. This study found Egyptian women had higher free estradiol levels than British women (73). Although inoperable, locally advanced and metastatic post-menopausal Egyptian and British cases responded similarly to endocrine therapy (tamoxifen alone or with prednisolone), Egyptian premenopausal cases responded poorly to endocrine therapy (oophorectomy with or without concurrent prednisolone), with the median time to progression three months (74).

Egyptian BC research has been aided by the creation of the Gharbiah population-based cancer registry (GCR) in 1998 as part of the Middle East Cancer Consortium (75). A number of GCR based studies have focused on IBC and urban/rural differences in BC incidence and hormone receptor status (76-80). A small case series of 48 Egyptian and 12 US IBC cases found the Egyptian cases had a higher percentage of cases presenting with peau d'orange, edema, and erythema (77% vs. 29%, $p=0.02$), more tumor emboli (mean 14.1 vs. 5.0, $p=0.01$), and high levels of RhoC (87% vs. 14%, $p=0.0003$) (77). Another recent Egyptian study compared 48 IBC to 64 non-IBC cases, and found that IBC patients had significantly lower parity, fewer palpable tumors, increased RhoC overexpression, and more tumor emboli (78). Using data from the GCR, Dey et al. found higher overall incidence of BC in urban areas, along with a higher incidence of ERP BC in urban areas, hypothesizing that higher exposure to xenoestrogens in urban women might be the cause (79, 80).

Other recent studies of BC in Egypt have focused on factors associated with stage at diagnosis (81, 82). A study of patients recruited from the Egyptian National Cancer Institute of Cairo and the Tanta Cancer Center (where the GCR is housed) found in a multivariate analysis that lack of BC related pain, lack of knowledge regarding breast self-examination, and longer travel time to a treatment facility were all associated or marginally associated with late stage at diagnosis (81). In another recent study of archived BC tissue from patients of the Universities of Cairo and Minia in Egypt, 44% of cases analyzed were of the luminal A subtype, which carries a favorable prognosis. However, the majority of cases presented with positive lymph nodes (71%) and tumors larger than two centimeters (85%), indicating that perhaps lack of early detection is to blame for the late stage at diagnosis and poor BC outcomes seen in Egypt (82).

Although some studies have suggested BC in premenopausal women from Egypt and other parts of North Africa are particularly aggressive, there have been few comprehensive evaluations of BC characteristics in Egypt. Therefore, the third study contained in this dissertation presents an age-stratified analysis of tumor grade, hormone receptor status, histology, and stage at diagnosis in Egypt's GCR for cases diagnosed from 2004 to 2008, with a comparison to US SEER cases over the same time period.

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Chapter 2

Association of Inflammatory and Non-Inflammatory Breast Cancer with Socioeconomic Characteristics in the Surveillance, Epidemiology, and End Results Database, 2000-2007

Introduction

Breast cancer is a heterogeneous disease, characterized by distinct tumor subtypes thought to correspond to different etiologies (1-5). Inflammatory breast cancer (IBC) is a rare and highly aggressive form of primary breast cancer (6-11). Although risk factors for IBC remain largely unknown, some studies have shown different risk factor profiles for IBC as compared to non-IBC cases (12-15).

Breast cancer incidence in the United States (US) is related to socioeconomic position (SEP) (16), with higher incidence among women with higher education and income (17, 18) and among women residing in communities with higher average levels of education and income (19-23). Although some studies have found much of this association can be explained by known breast cancer risk factors (17, 22), a study examining both individual- and community-level SEP revealed that after adjusting for individual SEP and breast cancer risk factors, women living in the highest SEP communities continued to have greater odds of having breast cancer compared to women living in the lowest SEP communities, suggesting community-level effects on breast cancer risk (16). Robert et al. hypothesized that these community effects could independently affect breast cancer risk through various pathways including more access

to mammograms (leading to more breast cancer detection) and community norms such as exogenous hormone use, alcohol intake, and diet (16).

Higher incidence of overall breast cancer in urban areas, both in the US and internationally, has been reported for many years (24-28). Residence is also related to SEP, with rural residents in the US generally having lower income, less education, and lower health insurance coverage than their urban counterparts (29).

Given the lack of knowledge regarding factors associated with IBC incidence, and the evidence that some overall breast cancer risk factors may not have the same effect on IBC risk, the aim of this study was to examine the association of county-level SEP measures to IBC and non-IBC incidence in the US Surveillance, Epidemiology, and End Results (SEER) database linked to 2000 US Census county-attribute data.

Materials and methods

Data Source

The SEER 17 Registries database linked to 2000 US county attributes was utilized for this analysis (30). The population-linked dataset includes all breast cancer cases from 2000-2007 for the following SEER registries: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San-Francisco-Oakland, Seattle-Puget Sound, Utah, Los-Angeles, San Jose-Monterey, rural Georgia, the Alaska Native Tumor Registry, Greater California, Kentucky, Louisiana, and New Jersey (31). The US SEER database covers approximately 26% of the US population, including 23% of African Americans, 40% of Hispanics, 42% of American Indians and Alaska Natives, 53% of Asians, and 70% of Hawaiian/Pacific Islanders (32).

Individual-Level Measures

The outcome variable for this analysis was diagnosis of a first malignant primary breast cancer (International Classification of Diseases for Oncology (ICD-O-3) = C500-C509) as IBC or non-IBC. In order to be certain all IBC cases were captured, a comprehensive case definition was used where a breast cancer case having any one of the following codes assigned to the SEER variables below was classified as IBC (6, 15, 33-35):

- Site and Morphology.Histologic Type ICD-O-3 (2000-2007) = 8530 (“Inflammatory Carcinoma”) (36, 37)
- Stage - TNM.Derived AJCC [American Joint Committee on Cancer] T, 6th ed (for cases 2004+) = T4d (“Inflammatory Carcinoma”) (36, 38)
- Extent of Disease [EOD] - CS.CS extension (for cases 2004+) = 71-73 (36, 39)
 - 71: “Diagnosis of inflammatory carcinoma without a clinical description of inflammation, erythema, edema, peau d’orange, etc., of more than 50% of the breast, with or without dermal lymphatic infiltration. Inflammatory carcinoma, NOS.”
 - 72: “Diagnosis of inflammatory carcinoma with a clinical description of inflammation, erythema, edema, peau d’orange, etc., of less than or equal to 50% of the breast, with or without dermal lymphatic infiltration.”
 - 73: “Diagnosis of inflammatory carcinoma with a clinical description of inflammation, erythema, edema, peau d’orange, etc., of more than 50% of the breast, with or without dermal lymphatic infiltration.”
- Extent of Disease - Historic.EOD 10 - extent (for cases 2000-2003) = 70 (36, 40)
 - 70: “Inflammatory carcinoma, including diffuse (beyond that directly overlying the tumor) dermal lymphatic permeation or infiltration”

All other histologic types were considered non-IBC. Breast cancers assigned to histologic codes 9590 and greater (lymphomas) were not included.

Age at diagnosis was analyzed as a continuous variable. A merged race and ethnicity variable with the following categories was also examined: Non-Hispanic White (NH White), Black, Hispanic White, Asian/Pacific Islander (API), and American Indian/Alaska Native (AI/AN).

County-Level Measures

Four county-level measures of SEP derived from the 2000 US census were used in this analysis (41). Counties were divided into metropolitan (metro) versus non-metro areas based on their 2003 US Department of Agriculture Rural-Urban Continuum code (RUCC), as has been done in previous cancer studies (42-45). Codes 1-3 were defined as metro counties, while codes 4-9 defined non-metro counties (code definitions below).

Rural-Urban Continuum Code Definitions for 2003 (46, 47):

Metro counties:

- 1 (Counties in metro areas of 1 million population or more)
- 2 (Counties in metro areas of 250,000 to 1 million population)
- 3 (Counties in metro areas of fewer than 250,000 population)

Non-metro counties:

- 4 (Urban population of 20,000 or more, adjacent to a metro area)
- 5 (Urban population of 20,000 or more, not adjacent to a metro area)
- 6 (Urban population of 2,500 to 19,999, adjacent to a metro area)
- 7 (Urban population of 2,500 to 19,999, not adjacent to a metro area)
- 8 (Completely rural or less than 2,500 urban population, adjacent to metro area)
- 9 (Completely rural or less than 2,500 urban population, not adjacent to a metro area)

Percent of persons within a county living below the federal poverty level was divided into three categories: <10%, 10%-19.99%, \geq 20%. This measure has been used in other SEER-based studies of SEP variation and disparities in cancer incidence and outcomes (48, 49). Percent of the population below the poverty level has several advantages as a SEP measure. It is easily understood, being based on readily interpretable variables with a priori cut-points, with areas having \geq 20% poverty generally considered “poverty areas” in census publications and studies using census data (48-51). Percent below the poverty level also takes into account a family’s size and age structure and is directly tied to the person’s ability to buy a representative basket of goods

and services, being updated annually by the US Census Bureau to reflect changes in the Consumer Price Index (48, 52).

Education, specifically completion of high school measured at both the individual and aggregate level, has been previously shown to be positively associated with overall breast cancer incidence (19, 53). In order to examine the county-level effect of high school education on IBC incidence, percent of adults (>25 years of age) in a county who did not graduate from high school was divided into quartiles based on the distribution of the variable across all counties in the US using the SEER county attributes database (54). The quartiles were as follows: $\leq 15.99\%$, 16-20.80%, 20.81-28.76%, $> 28.76\%$.

A composite measure of the poverty and education variables was created to examine their joint effect on the odds IBC vs. non-IBC incidence. The percent below high school graduate quartiles were combined with the 3-category poverty variable to create high, middle, and low SEP categories as follows: High SEP = $< 10.00\%$ poverty and $< 15.99\%$ less than high school graduate, Low SEP = 1) $10\% - 19.99\%$ poverty and $> 28.76\%$ less than high school graduate, or 2) $\geq 20\%$ poverty and $> 28.76\%$ less than high school graduate, or 3) $\geq 20\%$ poverty and 20.81-28.76% less than high school graduate, with the Middle SEP group being all remaining combinations. A similar index was used previously in a study examining overall breast cancer survival in the SEER database (43).

Statistical Analysis

Statistical software developed by the SEER program (SEER*stat version 6.6.2, National Cancer Institute, Bethesda, MD) readily allows for the calculation of incidence rates using the incidence dataset linked to county attribute and population data (55).

Female adult (18+ years of age) IBC and non-IBC incidence rates (IRs) for the period from 2000-2007 were calculated. IRs were directly age-adjusted to the 2000 US standard population (56, 57), and further stratified on the following county-level SEP measures: metro vs. non-metro residence, percent below poverty, and percent less than high school graduate, as well as race/ethnicity. Upper and lower 95% confidence intervals (CIs) around the IR ratios were used to test for statistical significance. A 95% IR ratio CI not including 1 was indicative of statistical significance at the 0.05 significance level (58). 95% CIs for the IRs and IR ratios were calculated using the method described in Tiwari et al. (59). While SEER*stat allows for the calculation of incidence rates stratified by county attribute measures, it does not allow for the calculation of incidence rates by a variable created from the merging of two county attributes, such as the poverty-high school index.

In order to directly compare the relationship between IBC to non-IBC cases' and SEP, hierarchical logistic regression models (HLMs) were fit using the SAS glimmix procedure (version 9.1; SAS Institute Inc., Cary, NC) (60). Women who reside in the same county may have similar, unmeasured characteristics, and therefore be more alike than individual women across different counties. Thus, it is important to take the intra-class correlation into account as ignoring it may lead to underestimation of the regression coefficient's standard error (61, 62). A hierarchical modeling structure allows for the examination of both individual- and county-level fixed effects as well as accounting for the effect due to clustering within counties through the addition of a random intercept, leading to more accurate standard error estimates (61-63).

Four separate HLMs were fit, with each model including one county-level SEP measure as well as age at diagnosis and merged race/ethnicity as independent variables. Age at diagnosis and race/ethnicity were included in all models due to their previously reported association with the incidence of different histopathologic types of breast cancer, specifically IBC (1, 6, 7, 15, 33, 64-66). All HLMs modeled the log odds ratio (OR) of IBC. The general model is outlined below where the county intercept becomes a linear combination of a grand mean (α), the county SEP fixed effect (γ), and county random effects (μ), with β_1 and β_2 being individual fixed effects (63):

$$\text{logit}(\pi_{ij}) = \alpha + \gamma(\text{SEP})_j + \mu_j + \beta_1 \text{Age}_{ij} + \beta_2 \text{Race/Ethnicity}_{ij}$$

Results

346,211 first primary breast cancer cases in women 18+ years of age diagnosed from 2000-2007 were available for this analysis. We excluded 39 cases missing county-level information and 2,545 cases missing race/ethnicity, leaving 343,627 cases. After these exclusions, there were 5,536 IBC and 338,091 non-IBC cases included in this analysis. In the model examining metro vs. non-metro counties, a further 394 cases were excluded due to missing RUCC, leaving 5,525 IBC and 337,708 non-IBC cases for analysis.

The mean age at diagnosis for IBC was 58.0 years vs. 60.7 years for non-IBC. The majority of IBC cases were of NH White race/ethnicity (67.0%), followed by Black (14.6%), Hispanic White (12.7%), API (5.1%), and AI/AN (0.7%). The comparable percentages for non-IBC were 75.0, 9.1, 8.6, 6.9, and 0.4%. 22.6% of IBC cases were classified as high SEP using the poverty-high school index, while 51.4% were middle

SEP and 26.0% low SEP. Using the same index, 27.3% of non-IBC cases were considered high SEP, 50.8% middle SEP, and 21.8% low SEP (Table 2.1).

Table 2.2 provides the age-adjusted IRs (per 100,000) and IR ratios for IBC according to SEP characteristics and race/ethnicity and Table 2.3 the corresponding results for non-IBC. There was no difference in the overall IBC IRs for metro vs. non-metro residence. When these rates were stratified by race/ethnicity, the only significant difference was for Blacks (metro IR=3.4, non-metro IR=4.8). The IBC IRs for counties where >10% of the residents were below the poverty level were generally significantly higher for all races combined, NH Whites, and Blacks. No significant difference was seen in IBC poverty stratified rates for Hispanic Whites, API, or AI/AN. The IBC IRs for counties where a higher percentage of the population had not graduated from high school followed a similar pattern as the poverty variable.

Non-IBC IRs for those living in non-metro counties were significantly lower for all races combined and NH Whites, but significantly higher for API and AI/AN race/ethnicity groups. There was no significant difference in the metro and non-metro IRs for Blacks and Hispanic Whites. Non-IBC IRs for those living in counties where >10% of the residents were below the poverty level were significantly lower for all races combined, NH Whites, Hispanic Whites, API, and AI/AN, with no significant difference in rates observed for Blacks. The non-IBC IRs for counties where a higher percentage of the population had not graduated from high school followed a similar pattern as the poverty variable.

Table 2.4 gives the ORs and 95% confidence intervals (CIs) for the four HLMs. In these models, which account for the clustering of cases within counties, after

adjustment for age at diagnosis and race/ethnicity, residing in a high poverty county ($\geq 20\%$), a county in the highest quartile of persons with less than a high school degree, and a low SEP county based on the poverty-high school index was significantly associated with higher odds of IBC (OR (95% CI) = 1.25 (1.09-1.43), 1.25 (1.10-1.42), and 1.26 (1.11-1.44), respectively). Younger age and Black, Hispanic White, and AI/AN race/ethnicity were also significantly associated with higher odds of IBC in all models, while API race/ethnicity was significantly associated with lower odds of IBC.

Discussion

Contrary to the previously reported positive association between urban residence, SEP, and overall breast cancer occurrence (16-28), this study found that living in a high poverty county ($\geq 20\%$), a county with a high percentage of less than high school graduates, and residing in a low SEP county as defined by the poverty-high school index were significantly associated with IBC, even after adjustment for age at diagnosis and race/ethnicity.

Prior studies examining overall breast cancer occurrence have found it to be associated with urban residence and higher SEP (16-28). However, the majority of breast cancers are non-IBC, and thus determining the relationship between IBC and SEP based on studies of all breast cancer types is difficult. This study used an inclusive definition to separately characterize IBC from all other breast cancer types, and then directly compared IBC to non-IBC through use of HLMs adjusting for age and race/ethnicity, in order to specifically examine SEP and its association with IBC as a distinct breast cancer entity.

Residing in a county with a large percent of persons below the poverty level, less than high school graduates, and in the low SEP group of the poverty-high school index were all associated with IBC in these analyses, suggesting that poverty and education are capturing similar aspects of SEP that affect IBC incidence. As SEP measures, poverty and education both act as a summary measure of a county's SEP and can be compared over time and across US geographic areas (50). While poverty and education are correlated, as each has been shown to be related to overall breast cancer incidence, they were included as separate SEP measures as well as in a combined index in this analysis (16-23, 67). Metro vs. non-metro area of residence at diagnosis captures various characteristics that can be directly and/or indirectly related to an individual's health, such as population density, geographic isolation, exposure to agriculture, industrial or commercial complexes, and proximity and access to health care services (68, 69). Furthermore, there are many ways to classify counties based on characteristics such as administrative units, land-use, and economic concepts (68). It is possible the definition of metro vs. non-metro used in this analysis does not capture specific factors that may be related to IBC, and thus explain the lack of association seen.

Although risk factors for IBC remain largely unknown, some studies have shown different risk factor profiles for IBC patients as compared to non-IBC patients. Chang et al. found that high BMI was significantly associated with increased risk of IBC, regardless of menopausal status (12). This is in contrast to overall breast cancer, where higher premenopausal weight has been shown to reduce risk (70). Chang et al. also found IBC patients were more likely to be premenopausal and have younger age at menarche and first birth as compared to non-IBC and non-breast cancer patients (12).

A study conducted in France by Le et al. found that IBC patients had a lower educational level, a higher BMI, a longer cumulative duration of breastfeeding, and included a greater proportion of non-European women as compared to non-IBC patients (13). A recent study of Egyptian breast cancer cases found IBC patients had significantly lower parity than non-IBC patients (14). Furthermore, a 2010 study based in Tunisia reported a rural predominance of IBC among the cases studied, and hypothesized the reduction in IBC seen in that country was due in part to increasing SEP (71).

In this analysis, IBC was associated with younger age and Black race/ethnicity, while API race/ethnicity was associated with lower odds of IBC, as found in previous studies (1, 6, 7, 15, 33, 64-66). White Hispanic and AI/AN race/ethnicity were also found to be significantly associated with IBC. A previous study showed no difference in the age-adjusted IBC IR between Hispanic and non-Hispanic women for cases diagnosed from 1994-1998 reported to the North American Association of Central Cancer Registries (64). However, this study did not classify Hispanic origin as mutually exclusive from other race/ethnicities, and used the more restrictive ICD-O-3 8530 code to define IBC (64). Younger age at IBC diagnosis has been reported for AI/AN women as compared to White women (6, 64), although no studies which directly compared the IRs or proportion of IBC between AI/AN women and other race/ethnicities were located.

The strengths of this study include the use of the US SEER database, 5 mutually exclusive race/ethnicity categories, a comprehensive definition of IBC, and a hierarchical modeling structure. The SEER program is considered the standard for cancer registry data quality worldwide (72). Quality control studies, including case-finding, recoding, and reliability studies are continually conducted by the SEER program to ensure data

included in the registries are accurate and collected and recorded in a uniform and timely manner across all registries (72). As IBC is a relatively rare diagnosis, the US SEER database, which covers 26% of the US population residing in varying regions and geographic areas with over-representation of minority groups, allows for the stratification of IBC incidence by SEP and race/ethnicity categories (32).

Previous studies have been limited to reporting IBC rates and proportions for a limited number of race/ethnicity categories, usually for White, Black, & Other, due to small numbers of cases as well as the manner in which this data was recorded by SEER (1, 7, 15, 33, 73). Beginning with the November 2005 SEER data submission, the algorithms for creating the race recode variables within the SEER database were revised, allowing for the examination of incidence for four race categories: White, Black, AI/AN, and API, as well as Hispanic ethnicity (73). The race and Hispanic ethnicity data can also now be merged in order to create mutually exclusive race/ethnicity categories (73). This allowed for the current analysis to report results for 5 mutually exclusive race/ethnicity categories, as opposed to the more limited race/ethnicity analyses in previous IBC studies.

IBC studies have been hampered by lack of a standard case definition (6, 11, 74). Previous studies have used the ICD-O 8530 designation to define IBC (7, 64, 65, 75, 76). ICD-O code 8530 is a pathologic designation requiring plugging of the dermal lymphatics with tumor emboli and does not consider clinical skin changes (6). However, this conservative IBC definition is not consistent with the current AJCC staging manual guidelines, and may underestimate the true incidence of IBC (6, 7, 64, 77). SEER EOD codes are based on a combined clinical and operative/pathologic assessment abstracted

from the pathology report, and allow for identification of IBC cases that do not have ICD-O 8530 as the pathologic diagnosis for years prior to 2004 (7). From 2004 forward, SEER includes a variable with derived AJCC staging, which allows for the identification of IBC cases defined as the primary tumor designation of “T4d” (35, 36). The comprehensive IBC definition used in this paper is similar to that used in recent IBC studies (6, 15, 33-35). Using this definition should help ensure less misclassification of IBC cases to the non-IBC group. Finally, use of a hierarchical modeling structure allows for the calculation of more accurate standard errors, thus adding confidence to any significant results found (61-63).

A few limitations should be noted when interpreting the results of this analysis. Though SEER data are broadly representative of the US population, cases recorded in the SEER database are more likely to be foreign born and urban as compared to the US population as measured in the 2000 census (78). There are also a relatively small number of AI/AN IBC cases available for this analysis (n=39), which is reflected in the wide 95% CIs around the IR and OR estimates for this race/ethnicity category. However, due to the US SEER’s large size and over 30 years of follow-up, it is generally considered to accurately represent the overall US cancer population (78).

Another limitation is the lack of individual-level SEP information in the US SEER database and the inherent ecologic bias in interpreting the results of this analysis at the individual-level. Any associations seen between county-level SEP and IBC occurrence may not necessarily hold were individual-level SEP available and used in the analysis (79). Therefore, the results of this analysis are better interpreted at the contextual level, i.e., the effect being measured is that of residing in a county with a

particular SEP characteristic, not that of the breast cancer cases' individual SEP. However, a study comparing census-level SEP measures to individual-level measures found they were similarly associated with individual-level health outcomes (52). Furthermore, the US SEER database linked to US census data provides a unique opportunity to conduct analyses stratified by race/ethnicity and county-level SEP measures on a relatively large number of IBC and non-IBC cases.

Overall breast cancer has been found to be positively associated with SEP, whereas in this analysis IBC was associated with lower SEP. One explanation for these results is that women of lower SEP may have less access to health care that would lead to early detection and the resultant neglected breast cancer develops into IBC. Some earlier IBC work suggested that it may be a subtype of locally advanced breast cancer rather than a distinct entity (80). However, the majority of recent studies on the epidemiology, clinical and prognostic characteristics, biology, and molecular genetics of IBC suggest it is likely a distinct biologic entity from other breast cancer (10, 12-15, 35, 81-84). Another explanation is that breast cancers occurring in women of lower SEP presenting with skin involvement are misdiagnosed as IBC (85, 86). However, there is little literature, especially in the US, suggesting women of lower SEP are at higher risk for IBC, so it is unlikely clinicians would be more likely to look for and diagnose (or misdiagnose) IBC disproportionately in women of lower SEP.

These results are in keeping with a growing amount of evidence showing IBC likely has a different risk factor profile than other breast cancers and is a distinct biologic entity (10, 12-15, 35, 81-84). Few studies have examined the epidemiology of rarer forms of breast cancer such as IBC, though studies that have suggest the general breast

cancer risk profile may not hold for rarer breast cancer subtypes (1, 65, 87). Further investigation into the etiology of IBC is needed in order to elucidate risk factors for the disease that would help guide prevention and screening programs, especially studies which examine individual and community-level associations between multiple SEP measures and IBC incidence. However, these results also indicate the need for studies designed to investigate the disparity of higher incidence of IBC in lower SEP groups and racial/ethnic minorities, as well as potential interventions to eliminate these differences. Furthermore, because treatment is especially urgent in IBC, design and implementation of strategies that would promote earlier IBC diagnosis among lower SEP groups and racial/ethnic minorities, which traditionally experience less access to early detection programs, would likely have a direct and favorable impact on their prognosis (88).

Table 2.1 Socioeconomic and Ethnic Background Characteristics of the SEER Study Population, 2000-2007

	Inflammatory Breast Cancer n and (%)	Non-Inflammatory Breast Cancer n and (%)
Mean Age at Diagnosis (SD)	58.0 (14.5)	60.7 (14.3)
Race/Ethnicity		
Non-Hispanic White	3,707 (67.0)	253,442 (75.0)
Black	806 (14.6)	30,780 (9.1)
Hispanic White	704 (12.7)	29,111 (8.6)
Asian/Pacific Islander	280 (5.1)	23,252 (6.9)
American Indian/AK Native	39 (0.7)	1,506 (0.4)
Residence at Diagnosis ^a		
Metro County	4,966 (89.9)	304,346 (90.1)
Non-Metro County	559 (10.1)	33,362 (9.9)
County-Level % Below Poverty		
<10.00%	1,917 (34.6)	134,331 (39.7)
10.00-19.99%	3,122 (56.4)	179,577 (53.1)
≥20.00%	497 (9.0)	24,183 (7.2)
County-Level % Less than High School Graduate		
≤15.99%	1,669 (30.2)	118,092 (34.9)
16-20.80%	1,699 (30.7)	107,849 (31.9)
20.81-28.76%	855 (15.4)	45,123 (13.4)
>28.76%	1,313 (23.7)	67,027 (19.8)
Poverty-High School Index:		
High SEP	1,250 (22.6)	92,447 (27.3)
Middle SEP	2,845 (51.4)	171,883 (50.8)
Low SEP	1,441 (26.0)	73,761 (21.8)

^a394 cases missing RUCC – Note: no other cases missing

Table 2.2 Age-Adjusted IBC Incidence Rates per 100,000 and Rate Ratios (95% CI) Stratified by County-Level SEP and Race/Ethnicity, 2000-2007

Variable	All Races Combined		Non-Hispanic White		Black	
	Incidence Rate	Rate Ratio	Incidence Rate	Rate Ratio	Incidence Rate	Rate Ratio
Metro	2.3 (2.3-2.4)		2.3 (2.2-2.4)		3.4 (3.2-3.7)	
Non-Metro	2.3 (2.1-2.5)	0.99 (0.90-1.08)	2.2 (2.0-2.4)	0.95 (0.85-1.05)	4.8 ^a (3.7-6.1)	1.40 (1.06-1.81)
County-Level % Below Poverty						
<10.00% ^d	2.2 (2.1-2.3)	1.00	2.2 (2.1-2.3)	1.00	2.8 (2.3-3.3)	1.00
10.00-19.99%	2.4 ^b (2.3-2.5)	1.12 (1.06-1.19)	2.4 ^b (2.3-2.5)	1.07 (1.00-1.15)	3.7 ^b (3.4-4.0)	1.31 (1.08-1.60)
≥20.00%	2.7 ^b (2.4-2.9)	1.24 (1.12-1.37)	2.5 (2.2-2.8)	1.12 (0.99-1.27)	3.7 ^b (3.0-4.5)	1.32 (1.01-1.72)
County-Level % Less than High School Graduate						
≤15.99% ^d	2.1 (2.0-2.2)	1.00	2.1 (2.0-2.2)	1.00	3.2 (2.8-3.8)	1.00
16-20.80%	2.3 ^c (2.2-2.4)	1.09 (1.02-1.17)	2.4 ^c (2.2-2.5)	1.11 (1.03-1.21)	3.4 (2.9-3.9)	1.04 (0.84-1.28)
20.81-28.76%	2.6 ^c (2.4-2.8)	1.23 (1.13-1.33)	2.5 ^c (2.3-2.7)	1.18 (1.06-1.31)	3.3 (2.9-3.8)	1.03 (0.84-1.27)
>28.76%	2.6 ^c (2.4-2.7)	1.20 (1.12-1.30)	2.5 ^c (2.4-2.7)	1.20 (1.09-1.32)	4.1 ^c (3.6-4.8)	1.28 (1.04-1.58)

Table 2.2 Age-Adjusted IBC Incidence Rates per 100,000 and Rate Ratios (95% CI) Stratified by County-Level SEP and Race/Ethnicity, 2000-2007
(Continued)

Variable	Hispanic White		Asian/Pacific Islander		American Indian/Alaska Native	
	Incidence Rate	Rate Ratio	Incidence Rate	Rate Ratio	Incidence Rate	Rate Ratio (95% CI)
Metro	2.4 (2.2-2.6)		1.3 (1.1-1.4)		1.2 (0.7-1.9)	
Non-Metro	2.6 (1.7-3.7)	1.05 (0.69-1.55)	1.4 (0.7-2.4)	1.08 (0.55-1.92)	1.6 (0.6-3.5)	1.35 (0.43-3.47)
County-Level % Below Poverty						
<10.00% ^d	2.3 (1.9-2.8)	1.00	1.2 (1.0-1.5)	1.00	2.5 (1.4-4.0)	1.00
10.00-19.99%	2.4 (2.2-2.6)	1.05 (0.85-1.30)	1.3 (1.1-1.5)	1.08 (0.84-1.39)	1.2 (0.6-2.1)	0.49 (0.22-1.08)
≥20.00%	2.7 (2.1-3.4)	1.18 (0.87-1.60)	0.8 (0.2-2.0)	0.62 (0.16-1.68)	1.3 (0.5-2.8)	0.55 (0.19-1.41)
County-Level % Less than High School Graduate						
≤15.99% ^d	2.0 (1.6-2.5)	1.00	1.2 (1.0-1.5)	1.00	2.3 (1.4-3.7)	1.00
16-20.80%	2.5 (2.2-2.9)	1.25 (0.96-1.64)	1.2 (1.0-1.4)	0.95 (0.70-1.28)	1.3 (0.4-2.9)	0.55 (0.16-1.46)
20.81-28.76%	2.4 (1.9-2.9)	1.17 (0.86-1.59)	1.6 (0.9-2.6)	1.29 (0.71-2.22)	0.9 (0.2-2.4)	0.40 (0.10-1.23)
>28.76%	2.5 (2.2-2.8)	1.24 (0.97-1.60)	1.4 (1.1-1.8)	1.13(0.82-1.56)	1.3 (0.6-2.6)	0.57 (0.22-1.35)

^aNon-Metro rate significantly different from Metro rate (p<0.05)

^bRate significantly different from <10.00% rate (p<0.05)

^cRate significantly different from ≤15.99% rate (p<0.05)

^dReferent Category for Rate Ratios

Table 2.3 Age-Adjusted Non-IBC Incidence Rates per 100,000 and Rate Ratios (95% CI) Stratified by County-Level SEP and Merged Race/Ethnicity, 2000-2007

Variable	All Races Combined		Non-Hispanic White		Black	
	Incidence Rate	Rate Ratio	Incidence Rate	Rate Ratio	Incidence Rate	Rate Ratio
Metro	144.4 (143.9-144.9)		158.7 (158.0-159.3)		136.3 (134.7-137.9)	
Non-Metro	135.5 ^a (134.0-137.0)	0.94 (0.93-0.95)	139.1 ^a (137.5-140.7)	0.88 (0.87-0.89)	131.6 (125.4-138.0)	0.97 (0.92-1.01)
County-Level % Below Poverty						
<10.00% ^d	151.9 (151.0-152.7)	1.00	159.5 (158.6-160.5)	1.00	135.1 (131.8-138.5)	1.00
10.00-19.99%	139.8 ^b (139.2-140.5)	0.92 (0.91-0.93)	155.7 ^b (154.8-156.6)	0.98 (0.97-0.98)	136.0 (134.1-137.9)	1.01 (0.98-1.04)
≥20.00%	129.9 ^b (128.2-131.5)	0.86 (0.84-0.87)	139.3 ^b (137.2-141.5)	0.87 (0.86-0.89)	137.4 (133.1-141.9)	1.02 (0.98-1.06)
County-Level % Less than High School Graduate						
≤15.99% ^d	151.2 (150.4-152.1)	1.00	158.6 (157.6-159.6)	1.00	135.9 (132.7-139.2)	1.00
16-20.80%	146.7 ^c (145.8-147.6)	0.97 (0.96-0.98)	158.8 (157.7-159.9)	1.00 (0.99-1.01)	137.6 (134.5-140.8)	1.01 (0.98-1.05)
20.81-28.76%	136.7 ^c (135.5-138.0)	0.90 (0.89-0.91)	147.1 ^c (145.4-148.7)	0.93 (0.92-0.94)	134.8 (132.0-137.7)	0.99 (0.96-1.02)
>28.76%	131.6 ^c (130.6-132.6)	0.87 (0.86-0.88)	152.7 ^c (151.2-154.2)	0.96 (0.95-0.97)	135.8 (132.5-139.1)	1.00 (0.97-1.03)

Table 2.3 Age-Adjusted Non-IBC Incidence Rates per 100,000 and Rate Ratios (95% CI) Stratified by County-Level SEP and Merged Race/Ethnicity, 2000-2007 (Continued)

Variable	Hispanic White		Asian/Pacific Islander		American Indian/Alaska Native	
	Incidence Rate	Rate Ratio	Incidence Rate	Rate Ratio	Incidence Rate	Rate Ratio
Metro	105.0 (103.7-106.3)		108.1 (106.6-109.5)		50.3 (46.8-53.9)	
Non-Metro	103.6 (97.5-110.0)	0.99 (0.93-1.05)	117.3 ^a (110.3-124.7)	1.09 (1.02-1.16)	70.3 ^a (62.2-79.3)	1.40 (1.21-1.61)
County-Level % Below Poverty						
<10.00% ^d	122.6 (119.4-125.8)	1.00	115.1 (112.8-117.4)	1.00	106.4 (98.2-115.0)	1.00
10.00-19.99%	101.5 ^b (100.1-103.0)	0.83 (0.80-0.85)	105.4 ^b (103.6-107.2)	0.92 (0.89-0.94)	47.3 ^b (43.3-51.6)	0.44 (0.40-0.50)
≥20.00%	98.2 ^b (94.5-102.0)	0.80 (0.77-0.84)	79.0 ^b (71.0-87.6)	0.69 (0.62-0.76)	52.8 ^b (46.4-59.8)	0.50 (0.43-0.58)
County-Level % Less than High School Graduate						
≤15.99% ^d	121.2 (117.7-124.7)	1.00	116.9 (114.3-119.5)	1.00	115.3 (107.4-123.7)	1.00
16-20.80%	113.2 ^c (110.7-115.8)	0.93 (0.90-0.97)	104.5 ^c (102.2-106.8)	0.89 (0.87-0.92)	46.7 ^c (40.7-53.2)	0.40 (0.35-0.47)
20.81-28.76%	101.2 ^c (98.0-104.5)	0.84 (0.80-0.87)	89.3 ^c (83.5-95.3)	0.76 (0.71-0.82)	45.3 ^c (38.9-52.5)	0.39 (0.33-0.46)
>28.76%	96.0 ^c (94.2-97.8)	0.79 (0.77-0.82)	107.4 ^c (104.7-110.2)	0.92 (0.89-0.95)	32.6 ^c (28.2-37.6)	0.28 (0.24-0.33)

^aNon-Metro rate significantly different from Metro rate (p<0.05)

^bRate significantly different from <10.00% rate (p<0.05)

^cRate significantly different from ≤15.99% rate (p<0.05)

^dReferent Category for Rate Ratios

Table 2.4 Odds Ratios (95% CI) from Four Hierarchical Logistic Regression Models Examining the Relationship between County-Level Sociodemographic Factors and Inflammatory Breast Cancer, SEER Program, 2000-2007^a

Model 1		Model 2		Model 3		Model 4	
Variable	OR (95% CI)	Variable	OR (95% CI)	Variable	OR (95% CI)	Variable	OR (95% CI)
Non-Metro ^b	1.00	County-Level % Below Poverty <10.00% ^b	1.00	County-Level % Less than High School Graduate ≤15.99% ^b	1.00	Poverty-High School Index: High SEP ^b	1.00
Metro	0.90 (0.81-1.00)	10.00-19.99%	1.06 (0.96-1.18)	16-20.80%	1.04 (0.93-1.17)	Middle SEP	1.10 (0.98-1.22)
Age at Diagnosis	0.99 (0.99-0.99)	≥20.00%	1.25 (1.09-1.43)	20.81-28.76%	1.11 (0.97-1.28)	Low SEP	1.26 (1.11-1.44)
Race/Ethnicity		Age at Diagnosis	0.99 (0.99-0.99)	Age at Diagnosis	0.99 (0.99-0.99)	Age at Diagnosis	0.99 (0.99-0.99)
NHWhite ^b	1.00	Race/Ethnicity		Race/Ethnicity		Race/Ethnicity	
Black	1.73 (1.59-1.87)	NHWhite ^b	1.00	NHWhite ^b	1.00	NHWhite ^b	1.00
Hispanic White	1.46 (1.34-1.59)	Black	1.70 (1.56-1.84)	Black	1.70 (1.57-1.85)	Black	1.70 (1.56-1.84)
API	0.79 (0.69-0.89)	Hispanic White	1.44 (1.32-1.57)	Hispanic White	1.44 (1.32-1.57)	Hispanic White	1.44 (1.32-1.57)
AI/AN	1.55 (1.06-2.26)	API	0.78 (0.69-0.89)	API	0.78 (0.69-0.89)	API	0.78 (0.69-0.89)
		AI/AN	1.59 (1.14-2.22)	AI/AN	1.62 (1.16-2.26)	AI/AN	1.61 (1.15-2.25)

^aAll variables in each column are mutually adjusted for each other

^bReferent Category

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Chapter 3

Inflammatory and Non-Inflammatory Breast Cancer Survival by Socioeconomic Position in the Surveillance, Epidemiology, and End Results Database, 1990-2008

Introduction

Inflammatory breast cancer (IBC), a rare and aggressive form of the disease, has been shown to have worse survival than other types of breast cancer (BC), even after adjustment for numerous individual and tumor characteristics and treatment (1-7). In clinical trials of neoadjuvant chemotherapy, IBC had worse prognosis than Stage III non-IBC both for increased loco-regional and distant recurrence rates and overall survival (8).

Although a few hospital and population-based studies have examined IBC survival by patient and tumor characteristics (2, 4, 5, 7, 9-12), only one population based study examined IBC survival by socioeconomic position (SEP) and race/ethnicity (11). This study included 935 incident cases of IBC (1998-2002) in the Florida Cancer Data System. The authors reported African American IBC cases had lower median survival than White IBC cases and also noted longer median survival for patients living in more affluent areas as classified by percentage of population living under the federal poverty line. However, this study only examined community poverty level and insurance status in addition to race/ethnicity as measures of SEP, and was limited to cases diagnosed in Florida, so may not be representative of IBC cases from across the United States (11).

Furthermore, hormone receptor (HR) status was not available, so the authors were unable to adjust their results for this important prognostic factor (11).

As IBC cases appear to have worse survival even after adjustment for individual, tumor, and treatment characteristics, this study sought to detect potential differences in stage III and IV IBC and non-IBC survival by SEP and metropolitan (metro) vs. non-metro residence in the United States (US) Surveillance, Epidemiology, and End Results (SEER) database linked to 1990 and 2000 census derived county attributes. Examining IBC and non-IBC survival by SEP and area of residence will aid in elucidating factors associated with the survival difference and thus, this study has important implications for the targeting of BC education and health care resources.

Materials and methods

Data Source

The SEER 17 Registries database linked to 1990 and 2000 US county attributes was utilized for this analysis (13). The US SEER database covers approximately 28% of the US population, including approximately 25% of Whites, 26% of African Americans, 41% of Hispanics, 43% of American Indians and Alaska Natives, 54% of Asians, and 71% of Hawaiian/Pacific Islanders (14).

Individual-Level Measures

The outcome variable for this analysis was BC specific survival in years, stratified by stage and inflammatory status (IBC vs. non-IBC). Cases were followed from date of diagnosis to date of death, loss to follow-up, or December 31, 2008, if still alive and not

lost to follow-up. As IBC is automatically at Stage IIIB or higher (IV) if metastatic at diagnosis, this analysis was limited to first malignant primary American Joint Committee on Cancer (AJCC) Stage III and IV IBC and non-IBC in women aged 18+ years (15). In order to be certain all IBC cases were captured, a comprehensive case definition was used where a breast cancer case having any one of the following codes assigned to the SEER*stat (version 7.0.5, National Cancer Institute, Bethesda, MD) variables below was classified as IBC, while all other cases were considered non-IBC (2, 4, 6, 7, 16, 17):

- Histologic Type ICD-O-3 (1990-2008) = 8530 (“Inflammatory Carcinoma”) (18, 19)
- Stage - Derived AJCC T, 6th ed (2004-2008) = T4d (“Inflammatory Carcinoma”) (15, 18)
- Extent of Disease [EOD] - CS extension (2004-2008) = 71-73 (18, 20)
 - 71: “Diagnosis of inflammatory carcinoma without a clinical description of inflammation, erythema, edema, peau d’orange, etc., of more than 50% of the breast, with or without dermal lymphatic infiltration. Inflammatory carcinoma, NOS.”
 - 72: “Diagnosis of inflammatory carcinoma with a clinical description of inflammation, erythema, edema, peau d’orange, etc., of less than or equal to 50% of the breast, with or without dermal lymphatic infiltration.”
 - 73: “Diagnosis of inflammatory carcinoma with a clinical description of inflammation, erythema, edema, peau d’orange, etc., of more than 50% of the breast, with or without dermal lymphatic infiltration.”
- Historic EOD 10 - extent (1990-2003) = 70 (18, 21)
 - 70: “Inflammatory carcinoma, including diffuse (beyond that directly overlying the tumor) dermal lymphatic permeation or infiltration.”

Other individual variables included in the analysis were age at diagnosis (analyzed as continuous), race/ethnicity (Non-Hispanic White (NH White), African American, Hispanic White, Asian/Pacific Islander (API), and American Indian/Alaska Native (AI/AN)), hormone receptor status, grade, receipt of surgery at primary BC site (yes/no), and receipt of any type of radiation therapy as part of the initial treatment plan (yes/no). Cases that were estrogen and/or progesterone receptor positive were classified

as hormone receptor positive (HRP), while cases not testing positive for either of these hormone receptors were considered hormone receptor negative (HRN). Estrogen and progesterone receptor status was determined by assay results in the medical record abstracted by SEER registries. In cases where assay results were reported for more than one tumor specimen, the highest value was recorded (if any sample is positive, the receptor is recorded as positive). SEER abstractors record assay results from tumor specimens prior to receipt of neoadjuvant therapy, although if not available, post-treatment results are reported. Cases where either assay was not ordered or performed, borderline and undetermined whether positive or negative, ordered – results not in chart, or where there was no documentation/information in the patient record were excluded (22). Although excluding cases where hormone receptor status is missing may potentially introduce selection bias, the large majority of cases (82%) had hormone receptor status recorded. Grade was dichotomized into low grade (well differentiated grade I and moderately differentiated grade II tumors) vs. high grade tumors (poorly differentiated grade III and undifferentiated; anaplastic grade IV tumors).

County-Level Measures

Three county-level measures of SEP derived from the 1990 and 2000 US censuses were used in this analysis (23). For both the 1990 and 2000 census, the percent of persons below the poverty level within a county was dichotomized to $<20\%$ vs. $\geq 20\%$. The 1990 poverty level and census result was applied to all cases diagnosed from 1990-1999, while the 2000 poverty level and census result was applied to cases diagnosed from 2000-2008.

SEP variation in survival was further examined in the subset of cases diagnosed from 2000-2008 by an index combining the percent of persons below the poverty level and the percent of persons who did not graduate from high school. The percent of adults greater than 25 years of age within a county who did not graduate from high school (based on 2000 US Census results) was divided into quartiles based on the distribution of the variable across all counties in the US using the SEER county attributes database (24). These high school quartiles were then combined with the poverty variable to create high and lower SEP categories as follows: High SEP = <10.00% poverty and \leq 15.99% less than high school graduate, Lower SEP = \geq 10% poverty and >15.99% less than high school graduate. This dichotomized index is based on one previously used to examine IBC incidence and BC survival (17, 25).

BC survival by metro vs. non-metro area of residence was also examined in the subset of cases diagnosed from 2000-2008. As in previous analyses, rural-urban continuum codes (RUCC) codes 1-3 (counties in metro areas of 1 million to fewer than 250,000) were defined as metro counties, while codes 4-9 (urban population of 20,000 or more, adjacent to a metro area to completely rural or <2,500 urban population, not adjacent to a metro area) defined non-metro counties (17, 25-28).

Statistical Analysis

Breast cancer specific (BCS) survival stratified on inflammatory status and stage was examined through use of the Kaplan-Meier estimator to compare survival curves by county-level SEP variables, with the log-rank test used to detect differences between the survival curves. Separate proportional hazards models were fit for each of the three

county-level SEP variables, stratified by inflammatory status and stage, in order to determine if the hazard of death from IBC as well as non-IBC differs by county-level SEP. All models were adjusted for age at diagnosis, race/ethnicity, hormone receptor status, tumor grade, and receipt of surgery and/or radiation. An alpha level ≤ 0.05 was used to determine statistical significance. Analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC).

Results

76,644 stage III and IV first malignant primary BCs diagnosed between 1990 and 2008 were available for this analysis. Six cases were excluded due to missing county-level information, 314 due to missing race/ethnicity, 13,827 due to missing hormone receptor status, 8,317 due to missing grade, 359 due to missing surgery information, and 2,148 due to missing radiation information, leaving 5,526 IBC and 46,147 non-IBC cases.

Table 3.1 provides the means and frequencies for the sociodemographic, tumor, and treatment characteristics of the study population. Both stages III and IV IBCs had lower mean ages than non-IBC: stage III IBC = 57.1 years vs. non-IBC = 57.8 years; stage IV IBC = 56.8 years vs. non-IBC = 61.2 years. A higher proportion of stage IV IBC was found in African Americans, Hispanic Whites, and AI/ANs as compared to stage IV non-IBC. Regardless of stage, IBC tended to have worse prognostic tumor characteristics compared to non-IBC, including less HRP and higher grade tumors. The majority of cases, regardless of stage and inflammatory status, resided in counties with <20% poverty.

For the sub-analysis of cases diagnosed from 2000-2008, 4,030 IBC and 36,148 non-IBC cases were included. Forty-two cases were missing RUCC, leaving 4,021 IBC and 36,115 non-IBC cases for the metro vs. non-metro county analysis. The majority of cases, regardless of stage or inflammatory status, resided in metro and lower SEP counties.

For cases diagnosed from 1990 to 2008, the median BCS survival for stage III IBC was 4.75 years (range: 0-18.8 years), while the median BCS survival for stage III non-IBC was much higher (13.4 years, range: 0-18.9 years), with the log-rank test indicating significant differences between the survival curves between stage III IBC and non-IBC ($p < 0.0001$). The median BCS survival for both stage IV IBC and non-IBC were much lower (1.75 years, range: 0-15.7 and 2.3 years, range: 0-18.9, respectively), with the log-rank test indicating significant differences between the survival curves of stage IV IBC and non-IBC as well ($p < 0.0001$).

The Kaplan-Meier survival curves (Figures 3.1-3.4) generally showed non-IBC cases residing in low poverty, high SEP, metro counties had better overall survival, with survival differences between IBC and non-IBC and SEP groups appearing to be larger for stage III cancers. Log-rank test statistics indicated significant survival differences ($p < 0.0001$) between the survival curves shown on each figure.

Figure 3.1 shows the BCS Kaplan-Meier survival curves for stage III IBC and non-IBC by county-level percent of persons below the poverty level for cases diagnosed from 1990 to 2008. The median BCS survival for stage III IBC cases residing in counties with $< 20\%$ poverty was 4.8 years (range: 0-18.8 years), while median BCS survival for stage III IBC cases in counties with $\geq 20\%$ poverty was 4.1 years (range: 0-17.2 years).

The corresponding values for non-IBC were 14.0 years (range: 0-18.9 years) and 10.6 years (range: 0-18.75 years), respectively.

Figure 3.2 shows the BCS Kaplan-Meier survival curves for stage IV IBC and non-IBC by county-level percent of persons below the poverty level for cases diagnosed from 1990 to 2008. The median BCS survival for stage IV IBC cases residing in counties with <20% poverty was 1.75 years (range: 0-15.7 years), while median BCS survival for stage IV IBC cases residing in counties with $\geq 20\%$ poverty was 1.6 years (range: 0-8.75 years). The corresponding values for non-IBC were 2.3 years (range: 0-18.9 years) and 2.0 years (range: 0-18.1 years), respectively.

Figure 3.3 shows the BCS Kaplan-Meier survival curves for stage III IBC and non-IBC by the county-level poverty-high school index for cases diagnosed from 2000 to 2008. The median BCS survival for stage III IBC cases residing in high SEP counties was 6.9 years (range: 0-8.9 years), while median BCS survival for stage III IBC cases in lower SEP counties was 5.2 years (range: 0-8.9 years). The median survival time for stage III non-IBC cases for both SEP groups had not been reached and therefore not estimated (range for both groups: 0-8.9 years).

Figure 3.4 shows the BCS Kaplan-Meier survival curves for stage IV IBC and non-IBC by the county-level poverty-high school index for cases diagnosed from 2000 to 2008. The median BCS survival for stage IV IBC cases residing in high SEP counties was 1.75 years (range: 0-7.2 years), while median BCS survival for stage IV IBC cases residing in lower SEP counties was 1.9 years (range: 0-8.75 years). The corresponding values for non-IBC were 2.6 years (range: 0-8.9 years) and 2.4 years (range: 0-8.9 years), respectively.

The median BCS survival for stage III IBC cases residing in metro counties was 5.5 years (range: 0-8.9 years), while median BCS survival for stage III IBC cases in non-metro counties was 5.9 years (range: 0-8.9 years). The median survival time for stage III non-IBC cases for both SEP groups had not been reached and therefore not estimated (range for both groups: 0-8.9 years). The median BCS survival for stage IV IBC cases residing in metro counties was 1.8 years (range: 0-8.75 years), while median BCS survival for stage IV IBC cases residing in non-metro counties was 2.3 years (range: 0-6.75 years). The corresponding values for non-IBC were 2.5 years (range: 0-8.9 years) and 2.2 years (range: 0-8.9 years), respectively (metro vs. non-metro Kaplan-Meier survival curves not shown).

Table 3.2 shows the Cox proportional hazards regression results for the hazard of BC death by inflammatory status, stage, and county-level percent below poverty. In general, residing in a county with $\geq 20\%$ persons below the poverty level appeared to increase the hazard of death, though the results were statistically significant only for stage III and IV non-IBC. Cases older in age and of African American race/ethnicity (as compared to NH White) also experienced a significantly higher hazard of death regardless of stage or inflammatory status. There was no significant difference in the Hispanic white, API, and AI/AN race/ethnicity groups hazard of death as compared to NH Whites, except among stage III non-IBC AI/AN cases (HR=1.40, 95% CI=1.06-1.86). High grade and HRN cancers both carried a significantly elevated hazard of death, while not receiving surgery at the BC site and not receiving radiation as part of the first course of treatment both elevated the hazard of BC death, though the radiation result was not significant among stage IV IBC cases.

Table 3.3 shows the Cox proportional hazards regression results for the hazard of BC death by inflammatory status, stage, and the county-level poverty-high school index for the subset of cases diagnosed between 2000 and 2008. The only group for which residing in a lower SEP county increased the hazard of death significantly was among stage III non-IBC cases. Similar to the results for percent below poverty, cases older in age and of African American race/ethnicity had a significantly higher hazard of death regardless of stage or inflammatory status, with no significant difference in the hazard of death for the other race/ethnicity groups. Having HRN cancer, high grade cancer, not receiving surgery at the BC site, and not receiving radiation as part of the first course of treatment all significantly increased the hazard of death, though the radiation result was not significant among stage IV IBC cases.

Table 3.4 shows the Cox proportional hazards regression results for the hazard of BC death by inflammatory status, stage, and metro vs. non-metro county of residence for the subset of cases diagnosed between 2000 and 2008. Although residing in a non-metro county appeared to increase the hazard of BC death, the result was significant only for stage III and IV non-IBC. Similar to the results for the other two county-level SEP measures, cases older in age and of African American race/ethnicity had a significantly higher hazard of death regardless of stage or inflammatory status, with no significant difference between the hazard of death for the other race/ethnicity groups. Also similar to previous results, having HRN cancer, high grade cancer, not receiving surgery at the BC site, and not receiving radiation as part of the first course of treatment all significantly increased the hazard of death, except for stage IV IBC cases.

Discussion

Similar to the Yang et al. 2009 study, this analysis showed that while unadjusted median survival generally appeared to be lower for those residing in lower SEP counties, after adjustment for age at diagnosis, race/ethnicity, tumor, and treatment characteristics, these survival differences were not significant for IBC (11). This analysis also similarly found that African American race/ethnicity was an independent predictor of the hazard of BC death for all cases (11).

IBC is a rare disease, comprising approximately 2% of all BC in the SEER database (2, 4), and, furthermore, it is difficult to detect using standard mammography techniques (29-31). It is therefore possible that, regardless of SEP, women and their health care providers tend to know less about this disease, and therefore it may be undetected and/or untreated for longer intervals in all SEP groups. In this regard, non-IBC cancers may be more likely to be detected earlier leading to a diagnostic biopsy and treatment. Therefore, women residing in lower SEP and more rural counties may experience a diagnostic and treatment delay leading to worse non-IBC survival if they have less access to health care. For example, in addition to less receipt of surgery, lower income, less educated women as well as those without private insurance are less likely to receive breast conserving surgery and more likely to receive mastectomies than their higher SEP counterparts (32-34). Furthermore, a recent study examining receipt of adjuvant chemotherapy and hormonal therapy adhering to National Comprehensive Cancer Network Clinical Practice Guidelines among women with locoregional BC found lack of insurance and residence in high poverty and/or low education areas were associated with receipt of non-guideline chemotherapy regimens, while living in a high

poverty area was associated with receipt of non-guideline hormonal therapy (35). In this analysis, there were significant differences in receipt of surgery and radiation treatment by race/ethnicity, with African Americans having the lowest receipt of surgery (81%) and radiation (47%) and Asian/Pacific Islanders having the highest (88% and 61%, respectively). While there were no differences in receipt of surgery by county-level poverty, cases residing in counties with $\geq 20\%$ poverty were less likely to receive radiation therapy (52%) as opposed to those residing in lower poverty counties (47%).

It should also be noted only stage III and IV cancers are examined in this analysis. SEP may play a more important role in earlier stage survival due to its association with early detection and treatment. In addition, there is in general no one single differing characteristic between guideline and non guideline therapies that was prominently missing in the patients of lower SEP.

Furthermore, most recent studies suggest IBC is a distinct biologic entity from other BCs, with these biologic differences likely contributing to poorer IBC survival (6, 7, 36-43). For instance, typical characteristics of IBC include wide dissemination of tumor cells throughout the breast and associated dermal lymphatics leading to acute onset of clinical signs such as erythema, edema, and breast tenderness and/or pain, as compared to most non-advanced non-IBC's which do not usually carry these same symptoms (9). Other IBC histologic/biologic features such as tumors that are rapidly progressive, highly angiogenic and angioinvasive and of high histologic grade with atypical mitotic figures, likely lead to IBC's propensity for metastasis and otherwise worse prognosis than non-IBC tumors (39).

As in this analysis, African Americans have previously been found to have worse BC and specifically, IBC survival (4, 5, 44-46). Interestingly, the effect of African American race/ethnicity on poorer survival held even after adjustment for county-level SEP, age at diagnosis, tumor and treatment characteristics. Some previous studies have shown the effect of African American race/ethnicity on BC survival is largely eliminated after adjustment for SEP, while others have shown the effect is independent of certain SEP measures (44, 46-49). A 2002 study of BC cases in the Metro Detroit SEER registry linked to Michigan Medicaid enrollment files found that after adjustment for age at diagnosis, marital status, stage, Medicaid enrollment, census tract percent below poverty, and surgery type, being African American was no longer associated with poorer survival as compared to White women (49). However, a 2002 meta-analysis of fourteen studies found African American race/ethnicity was an independent predictor of BC mortality after adjustment for SEP, stage, and age at diagnosis (46).

SEP encompasses a large array of characteristics, some easily measured and accounted for and others which can only readily be analyzed through proxy measures. It is possible this analysis does not use the SEP measure(s) most associated with IBC and African American race/ethnicity BC survival. Although there are a multitude of SEP measures and indices available, in the US, poverty level and education have the advantage of being easily understood and comparable across time and geographic areas (50). Furthermore, the poverty-level cut-point and poverty-high school index used in this analysis have been used in previous studies of cancer survival, with areas having $\geq 20\%$ poverty generally considered “poverty areas” in census publications (25, 51-53).

Numerous studies have found African American women are more often diagnosed with adverse prognostic characteristics, such as diagnosis at later stage, younger age, and having tumors that are more likely to be estrogen receptor negative and high grade (54-62). While these characteristics are correlated with the inferior survival seen in African American women, it is also likely that SEP-related factors, such as reproductive history, diet, physical activity, medical co-morbidities, and access to BC screening and treatment also play an important role (46).

No studies have examined IBC vs. non-IBC BCS survival by SEP in a nationwide, population based tumor registry. A major strength of this study is the use of the SEER database linked to 1990 and 2000 US census derived county-level attributes. The SEER program is considered to be the “gold” standard for data quality worldwide, with rigorous quality control, reliability, and completeness of data recorded timely and uniformly (63). As IBC is a rare form of BC, the SEER data linked to county attributes offers a unique opportunity to examine IBC survival stratified on county-level SEP characteristics, as well as other tumor and treatment characteristics included in the database. Furthermore, as the SEER program oversamples US minority groups, analyses are also able to be stratified on multiple race/ethnicity groups (14).

Another strength of this study is the use of a comprehensive IBC case definition. IBC is primarily a clinical diagnosis (29-31, 64, 65). Previous studies have used only the ICD-O 8530 histology code to identify IBC cases, which does not consider clinical skin changes and is not consistent with current AJCC staging guidelines (2, 5, 66, 67). In this analysis, we used SEER EOD codes for cases prior to 2004 as well as the SEER derived AJCC staging for cases 2004 forward in order to help ensure cases meeting AJCC staging

clinical criteria are included, as previous studies using only the ICD-O histologic code 8530 may have underestimated the number of IBC cases (2, 5, 66, 67).

This study has several limitations which should be noted. As the SEER database does not contain information on chemotherapy or hormonal treatment, we were unable to adjust for these important prognostic factors. It is also likely that changes in treatment over time have improved survival for those more recently diagnosed. Major advances in chemotherapy, surgery, and radiotherapy have been implemented during the period from 1990-2008 encompassing our analysis. (29-31, 64, 65, 68). However, it is unknown how quickly each of these therapies have been implemented in the community setting. The sub-analysis from 2000-2008 examining the poverty-high school index and metro vs. non-metro residence had similar results to the poverty analysis and involved a shorter time period, and thus is less likely to be affected by secular treatment trends. Furthermore, the SEER program is considered to accurately represent the US cancer population treated in various academic and community settings across the country, and therefore can provide an overall picture of BC survival in the US (69).

Another limitation of this study is the inherent ecologic bias when county-level SEP is interpreted as individual-level SEP. An individual's SEP may have a different effect on BC survival than that seen for county-level SEP measures (70). Therefore, these results are better viewed as the effect of residing in a county with a particular SEP measure on BCS survival rather than that of an individual's SEP. However, a previous study found census-level SEP measures have a similar association with individual-level health outcomes as individual SEP (71).

In conclusion, our results indicate IBC has worse survival than non-IBC, most pronounced for stage III cancers, and that residing in a lower SEP, non-metro county may worsen BCS survival, though this result was only significant for non-IBC in multivariate proportional hazards models. African Americans appear to have worse BCS survival regardless of inflammatory status, stage, county-level SEP, tumor, or treatment characteristics. Future research should examine multiple SEP measures and indices, both at the individual and community level, in order to better elucidate potential relationships between SEP and BC survival that will greatly aid in the targeting of BC, and specifically IBC, education, screening, and treatment programs. As this analysis and others have found generally poorer survival for IBC, regardless of SEP or race/ethnicity, it is important that IBC education interventions target women in various SEP and race/ethnicity groups. Finally, as this study and others indicate that African Americans experience poorer BC survival, programs designed specifically for African American women would be especially helpful (72).

Table 3.1 Sociodemographic, Tumor, and Treatment Characteristics of the SEER Study Population, 1990-2008

	Inflammatory Breast Cancer n and (%)		Non-Inflammatory Breast Cancer n and (%)	
	Stage III	Stage IV	Stage III	Stage IV
Mean Age at Diagnosis (SD)	57.1 (14.5)	56.8 (13.3)	57.8 (14.8)	61.2 (14.4)
Race/Ethnicity				
Non-Hispanic White	3,124 (70.3)	675 (62.2)	22,221 (67.6)	9,305 (70.1)
African American	532 (12.0)	197 (18.2)	4,201 (12.8)	1,863 (14.0)
Hispanic White	518 (11.7)	142 (13.1)	3,804 (11.6)	1,180 (8.2)
Asian/Pacific Islander	227 (5.1)	62 (5.7)	2,467 (7.5)	850 (6.4)
Am. Indian/AK Native	40 (0.90)	9 (0.83)	174 (0.53)	82 (0.62)
Hormone Receptor Status				
Positive	2,447 (55.1)	618 (57.0)	23,617 (71.9)	9,655 (72.7)
Negative	1,994 (44.9)	467 (43.0)	9,250 (28.1)	3,625 (27.3)
Grade				
Low (I/II)	1,187 (26.7)	287 (26.5)	13,995 (42.6)	5,704 (43.0)
High (III/IV)	3,254 (73.3)	798 (73.5)	18,872 (57.4)	7,576 (57.0)
Surgery at BC site				
Yes	4,048 (91.2)	597 (55.0)	31,842 (96.9)	7,788 (58.6)
No	393 (8.8)	488 (45.0)	1,025 (3.1)	5,492 (41.4)
Radiation Therapy				
Yes	2,659 (59.9)	467 (43.0)	18,717 (57.0)	5,147 (38.8)
No	1,782 (40.1)	618 (57.0)	14,150 (43.0)	8,133 (61.2)
% Below Poverty in County				
<20.00%	4,092 (92.1)	1,005 (92.6)	30,263 (92.1)	12,193 (91.8)
≥20.00%	349 (7.9)	80 (7.4)	2,604 (7.9)	1,087 (8.2)
Sub-Analysis of Cases Diagnosed from 2000-2008				
Poverty-High School Index:				
High SEP	768 (24.5)	199 (22.4)	6,741 (25.6)	2,651 (26.9)
Lower SEP	2,372 (75.5)	691 (77.6)	19,562 (74.4)	7,194 (73.1)
Residence at Diagnosis ^a				
Metro County	2,799 (89.3)	800 (90.1)	23,821 (90.6)	8,906 (90.5)
Non-Metro County	334 (10.7)	88 (9.9)	2,457 (9.4)	931 (9.5)

^a42 cases missing RUCC

Figure 3.1 Breast Cancer Specific Kaplan-Meier Survival Curves for Stage III IBC and Non-IBC by % Persons Below Poverty in County, 1990-2008

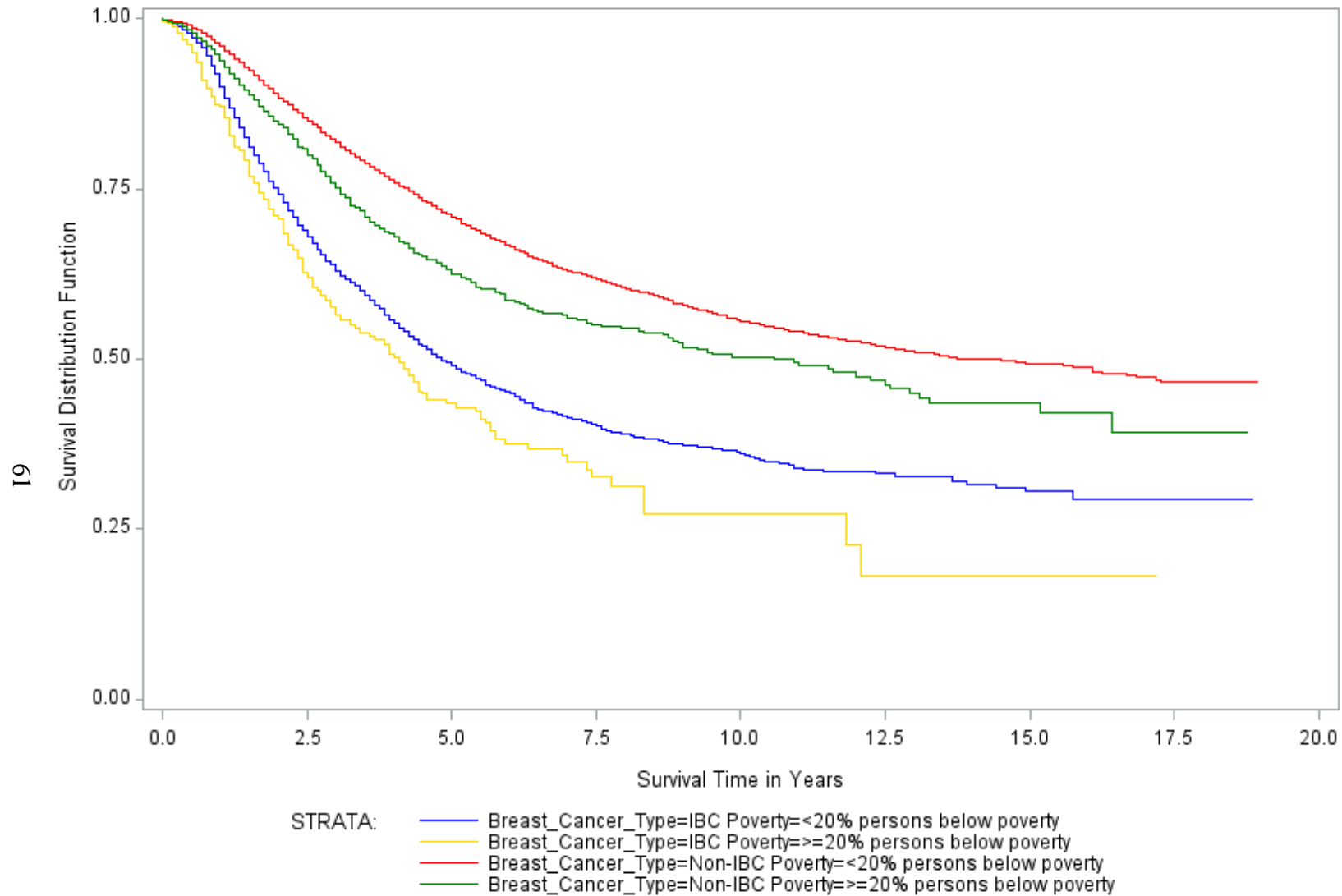


Figure 3.2 Breast Cancer Specific Kaplan-Meier Survival Curves for Stage IV IBC and Non-IBC by % Persons Below Poverty in County, 1990-2008

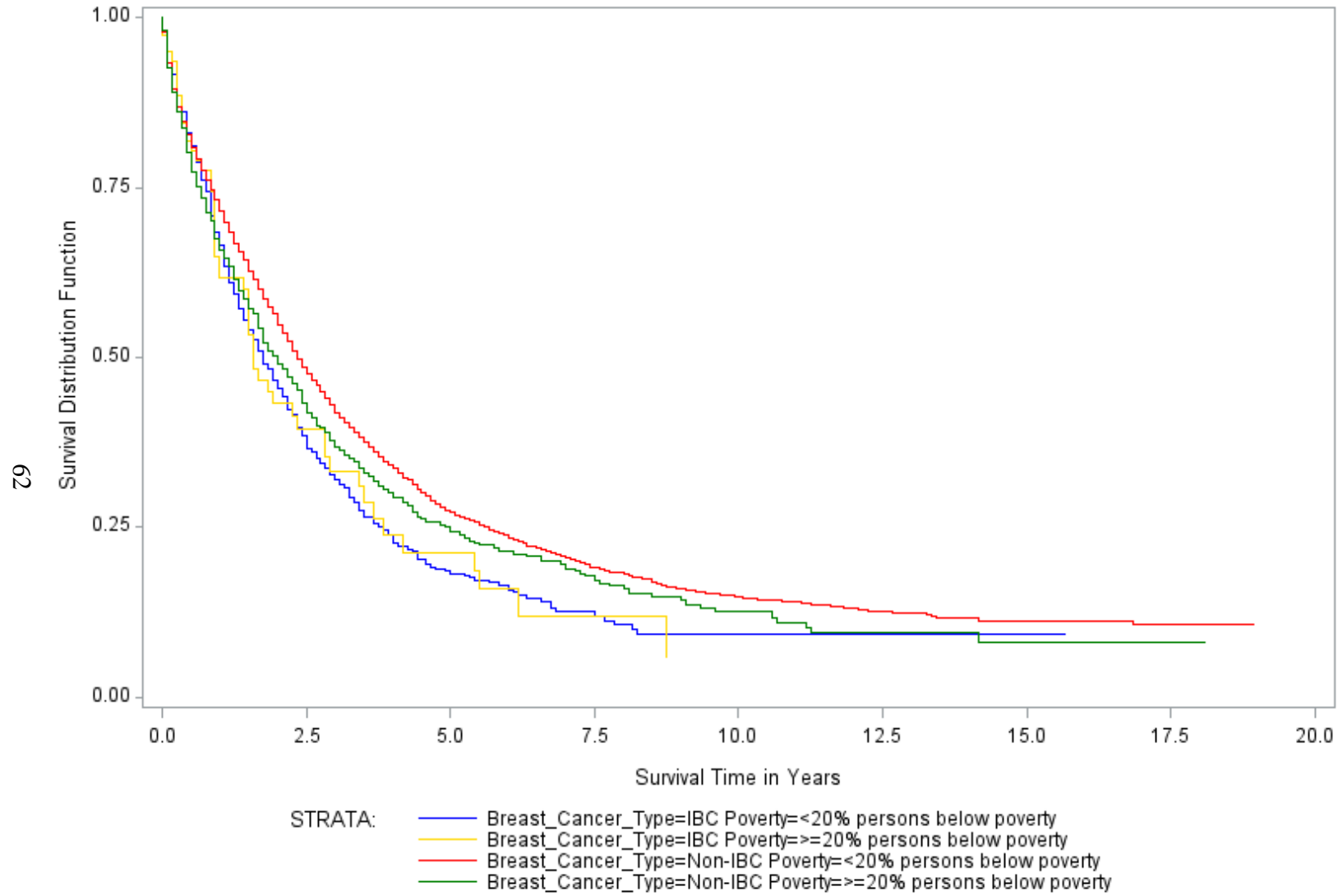


Figure 3.3 Breast Cancer Specific Kaplan-Meier Survival Curves for Stage III IBC and Non-IBC by Poverty-High School Index, 2000-2008

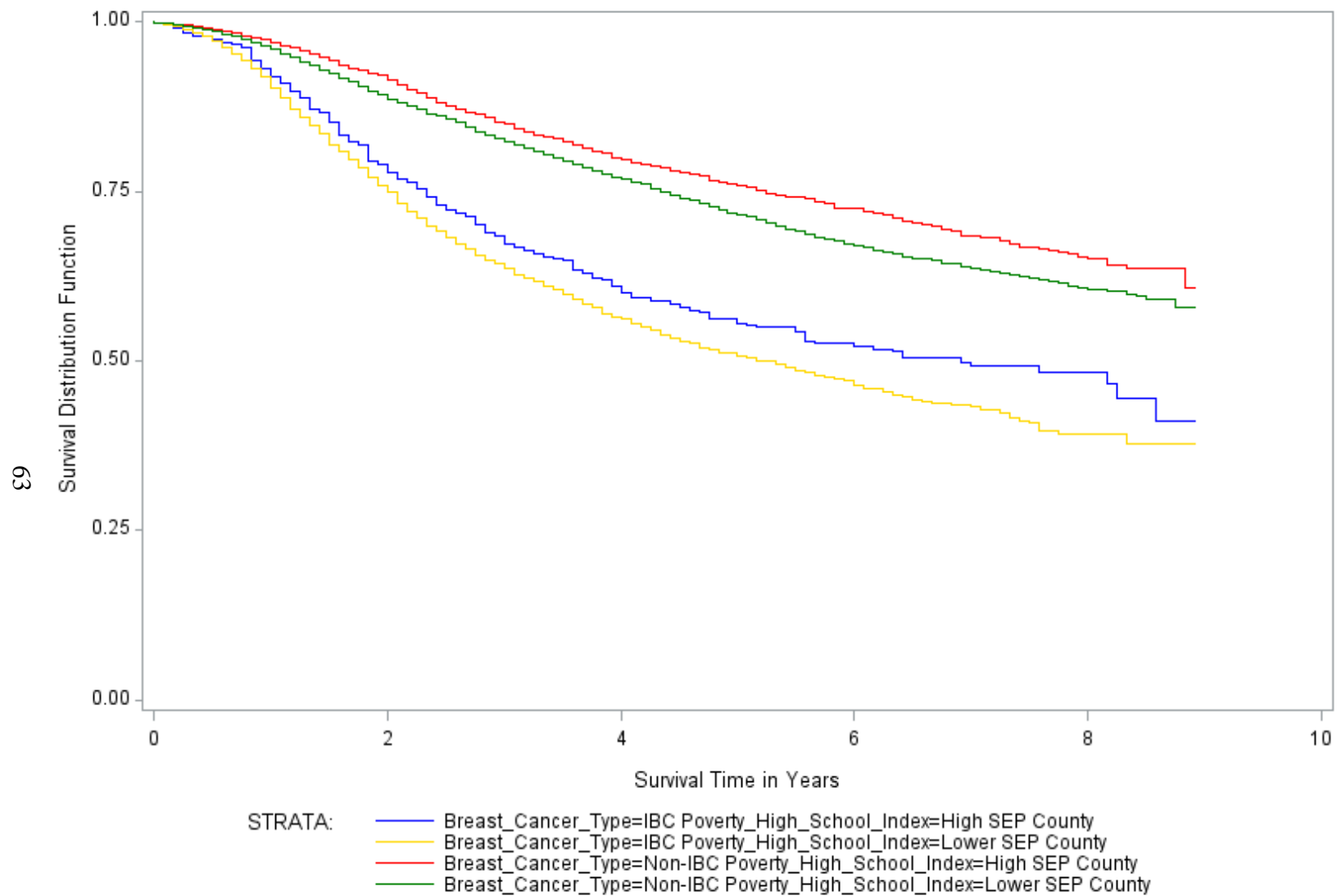
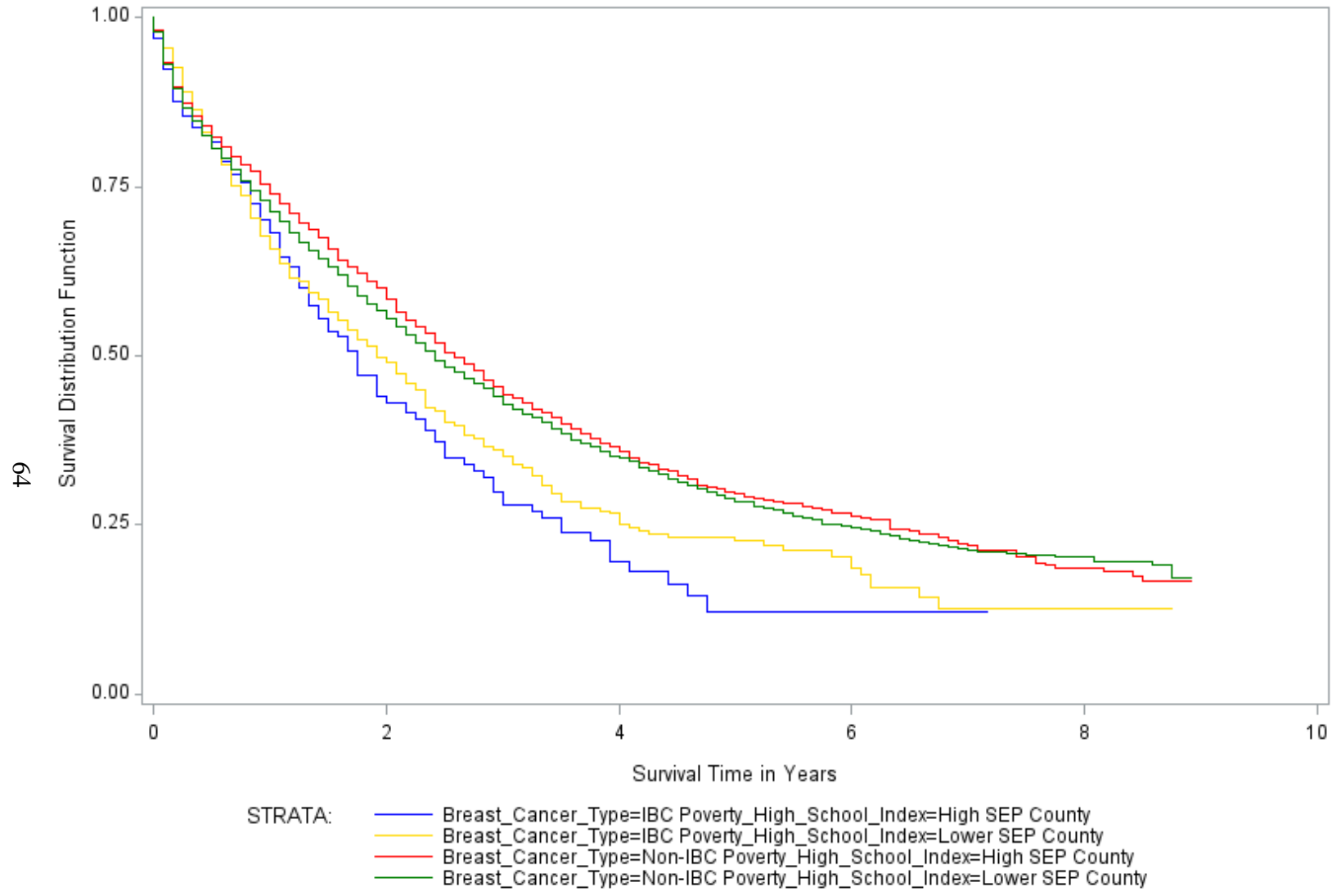


Figure 3.4 Breast Cancer Specific Kaplan-Meier Survival Curves for Stage IV IBC and Non-IBC by Poverty-High School Index, 2000-2008



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Table 3.2 Hazard Ratios (95% CI) from Four Cox Proportional Hazards Regression Models Examining the Relationship between County-Level Percent of Persons Below the Poverty Level, Breast Cancer Type, Stage and the Hazard of Breast Cancer Death, SEER Program, 1990-2008^a

Model 1: Stage III IBC		Model 2: Stage III Non-IBC		Model 3: Stage IV IBC		Model 4: Stage IV Non-IBC	
Variable	HR (95% CI)	Variable	HR (95% CI)	Variable	HR (95% CI)	Variable	HR (95% CI)
County-Level % Below Poverty <20.00% ^b	1.00	County-Level % Below Poverty <20.00% ^b	1.00	County-Level % Below Poverty <20.00% ^b	1.00	County-Level % Below Poverty <20.00% ^b	1.00
≥20.00%	1.13 (0.97-1.32)	≥20.00%	1.13 (1.05-1.22)	≥20.00%	1.05 (0.79-1.39)	≥20.00%	1.12 (1.03-1.21)
Age at Diagnosis	1.01 (1.00-1.01)	Age at Diagnosis	1.02 (1.01-1.02)	Age at Diagnosis	1.01 (1.01-1.02)	Age at Diagnosis	1.02 (1.02-1.02)
Race/Ethnicity NHWhite ^b	1.00	Race/Ethnicity NHWhite ^b	1.00	Race/Ethnicity NHWhite ^b	1.00	Race/Ethnicity NHWhite ^b	1.00
African American	1.46 (1.29-1.66)	African American	1.41 (1.32-1.50)	African American	1.36 (1.12-1.64)	African American	1.23 (1.15-1.31)
Hispanic White	0.99 (0.85-1.14)	Hispanic White	1.00 (0.92-1.08)	Hispanic White	0.95 (0.75-1.21)	Hispanic White	0.99 (0.91-1.07)
API	0.87 (0.71-1.08)	API	0.94 (0.86-1.03)	API	1.01 (0.71-1.42)	API	0.93 (0.85-1.02)
AI/AN	0.96 (0.61-1.50)	AI/AN	1.40 (1.06-1.86)	AI/AN	1.35 (0.56-3.29)	AI/AN	1.19 (0.91-1.57)
Hormone Receptor Status Positive ^b	1.00	Hormone Receptor Status Positive ^b	1.00	Hormone Receptor Status Positive ^b	1.00	Hormone Receptor Status Positive ^b	1.00
Negative	1.73 (1.58-1.89)	Negative	1.88 (1.79-1.97)	Negative	1.67 (1.43-1.95)	Negative	1.68 (1.60-1.77)
Grade Low (I/II) ^b	1.00	Grade Low (I/II) ^b	1.00	Grade Low (I/II) ^b	1.00	Grade Low (I/II) ^b	1.00
High (III/IV)	1.58 (1.42-1.77)	High (III/IV)	1.64 (1.56-1.73)	High (III/IV)	1.41 (1.17-1.71)	High (III/IV)	1.36 (1.30-1.43)
Surgery at BC site Yes ^b	1.00	Surgery at BC site Yes ^b	1.00	Surgery at BC site Yes ^b	1.00	Surgery at BC site Yes ^b	1.00
No	2.06 (1.79-2.37)	No	2.75 (2.49-3.03)	No	1.72 (1.47-2.01)	No	1.76 (1.68-1.84)
Radiation Therapy Yes ^b	1.00	Radiation Therapy Yes ^b	1.00	Radiation Therapy Yes ^b	1.00	Radiation Therapy Yes ^b	1.00
No	1.37 (1.25-1.50)	No	1.39 (1.32-1.45)	No	1.10 (0.94-1.29)	No	1.07 (1.02-1.12)

^aAll variables in each column are mutually adjusted for each other

^bReferent Category

Table 3.3 Hazard Ratios (95% CI) from Four Cox Proportional Hazards Regression Models Examining the Relationship between the County-Level Poverty-High School Index, Breast Cancer Type, Stage and the Hazard of Breast Cancer Death, SEER Program, 2000-2008^a

Model 1: Stage III IBC		Model 2: Stage III Non-IBC		Model 3: Stage IV IBC		Model 4: Stage IV Non-IBC	
Variable	HR (95% CI)	Variable	HR (95% CI)	Variable	HR (95% CI)	Variable	HR (95% CI)
Poverty-High School Index: High SEP ^b	1.00	Poverty-High School Index: High SEP ^b	1.00	Poverty-High School Index: High SEP ^b	1.00	Poverty-High School Index: High SEP ^b	1.00
Lower SEP	1.09 (0.95-1.25)	Lower SEP	1.10 (1.02-1.18)	Lower SEP	0.86 (0.69-1.06)	Lower SEP	1.04 (0.98-1.11)
Age at Diagnosis	1.01 (1.01-1.01)	Age at Diagnosis	1.02 (1.02-1.02)	Age at Diagnosis	1.01 (1.01-1.02)	Age at Diagnosis	1.02 (1.02-1.02)
Race/Ethnicity NHWhite ^b	1.00	Race/Ethnicity NHWhite ^b	1.00	Race/Ethnicity NHWhite ^b	1.00	Race/Ethnicity NHWhite ^b	1.00
African American	1.57 (1.34-1.85)	African American	1.36 (1.25-1.47)	African American	1.50 (1.20-1.87)	African American	1.27 (1.18-1.37)
Hispanic White	0.98 (0.82-1.18)	Hispanic White	1.02 (0.92-1.12)	Hispanic White	1.12 (0.85-1.48)	Hispanic White	1.06 (0.96-1.16)
API	0.94 (0.71-1.24)	API	0.93 (0.82-1.05)	API	0.90 (0.59-1.37)	API	0.88 (0.78-1.00)
AI/AN	0.82 (0.43-1.59)	AI/AN	1.00 (0.64-1.57)	AI/AN	1.36 (0.50-3.66)	AI/AN	1.13 (0.81-1.56)
Hormone Receptor Status Positive ^b	1.00	Hormone Receptor Status Positive ^b	1.00	Hormone Receptor Status Positive ^b	1.00	Hormone Receptor Status Positive ^b	1.00
Negative	2.05 (1.82-2.32)	Negative	2.25 (2.11-2.40)	Negative	1.68 (1.40-2.01)	Negative	1.75 (1.65-1.86)
Grade Low (I/II) ^b	1.00	Grade Low (I/II) ^b	1.00	Grade Low (I/II) ^b	1.00	Grade Low (I/II) ^b	1.00
High (III/IV)	1.51 (1.30-1.75)	High (III/IV)	1.74 (1.62-1.86)	High (III/IV)	1.52 (1.22-1.90)	High (III/IV)	1.37 (1.29-1.45)
Surgery at BC site Yes ^b	1.00	Surgery at BC site Yes ^b	1.00	Surgery at BC site Yes ^b	1.00	Surgery at BC site Yes ^b	1.00
No	2.05 (1.72-2.45)	No	2.96 (2.64-3.33)	No	1.89 (1.57-2.28)	No	1.90 (1.79-2.00)
Radiation Therapy Yes ^b	1.00	Radiation Therapy Yes ^b	1.00	Radiation Therapy Yes ^b	1.00	Radiation Therapy Yes ^b	1.00
No	1.43 (1.27-1.62)	No	1.47 (1.38-1.56)	No	1.06 (0.88-1.29)	No	1.06 (1.00-1.12)

^aAll variables in each column are mutually adjusted for each other

^bReferent Category

Table 3.4 Hazard Ratios (95% CI) from Four Cox Proportional Hazards Regression Models Examining the Relationship between Metro vs. Non-Metro County of Residence, Breast Cancer Type, Stage and the Hazard of Breast Cancer Death, SEER Program, 2000-2008^a

Model 1: Stage III IBC		Model 2: Stage III Non-IBC		Model 3: Stage IV IBC		Model 4: Stage IV Non-IBC	
Variable	HR (95% CI)	Variable	HR (95% CI)	Variable	HR (95% CI)	Variable	HR (95% CI)
County of Residence Metro ^b	1.00	County of Residence Metro ^b	1.00	County of Residence Metro ^b	1.00	County of Residence Metro ^b	1.00
Non-Metro	1.07 (0.89-1.29)	Non-Metro	1.20 (1.09-1.32)	Non-Metro	1.02 (0.76-1.38)	Non-Metro	1.21 (1.11-1.33)
Age at Diagnosis	1.01 (1.01-1.01)	Age at Diagnosis	1.02 (1.02-1.02)	Age at Diagnosis	1.01 (1.01-1.02)	Age at Diagnosis	1.02 (1.02-1.02)
Race/Ethnicity NHWhite ^b	1.00	Race/Ethnicity NHWhite ^b	1.00	Race/Ethnicity NHWhite ^b	1.00	Race/Ethnicity NHWhite ^b	1.00
African American	1.61 (1.37-1.89)	African American	1.39 (1.29-1.51)	African American	1.45 (1.17-1.80)	African American	1.30 (1.21-1.40)
Hispanic White	1.00 (0.84-1.20)	Hispanic White	1.05 (0.96-1.16)	Hispanic White	1.08 (0.83-1.42)	Hispanic White	1.08 (0.98-1.19)
API	0.95 (0.72-1.26)	API	0.94 (0.83-1.06)	API	0.88 (0.58-1.34)	API	0.89 (0.79-1.01)
AI/AN	0.57 (0.24-1.38)	AI/AN	1.01 (0.62-1.65)	AI/AN	0.90 (0.22-3.64)	AI/AN	1.14 (0.81-1.61)
Hormone Receptor Status Positive ^b	1.00	Hormone Receptor Status Positive ^b	1.00	Hormone Receptor Status Positive ^b	1.00	Hormone Receptor Status Positive ^b	1.00
Negative	2.06 (1.83-2.33)	Negative	2.25 (2.11-2.40)	Negative	1.68 (1.40-2.02)	Negative	1.75 (1.65-1.86)
Grade Low (I/II) ^b	1.00	Grade Low (I/II) ^b	1.00	Grade Low (I/II) ^b	1.00	Grade Low (I/II) ^b	1.00
High (III/IV)	1.50 (1.29-1.73)	High (III/IV)	1.74 (1.62-1.87)	High (III/IV)	1.52 (1.22-1.90)	High (III/IV)	1.37 (1.29-1.45)
Surgery at BC site Yes ^b	1.00	Surgery at BC site Yes ^b	1.00	Surgery at BC site Yes ^b	1.00	Surgery at BC site Yes ^b	1.00
No	2.07 (1.73-2.46)	No	2.98 (2.65-3.34)	No	1.90 (1.58-2.29)	No	1.91 (1.80-2.01)
Radiation Therapy Yes ^b	1.00	Radiation Therapy Yes ^b	1.00	Radiation Therapy Yes ^b	1.00	Radiation Therapy Yes ^b	1.00
No	1.44 (1.27-1.62)	No	1.48 (1.39-1.57)	No	1.06 (0.88-1.29)	No	1.06 (1.00-1.12)

^aAll variables in each column are mutually adjusted for each other

^bReferent Category

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Chapter 4

Age Stratified Comparison of Breast Cancer in the Egyptian Population-Based Registry and the United States Surveillance, Epidemiology, and End Results Program (2004-2008)

Introduction

Breast cancer (BC) in young women in the United States (US) is a relatively rare occurrence (1). However, BC is the leading cause of cancer death in adult women less than 60 years of age in high-income countries (2). Furthermore, numerous studies have reported BCs in young women tend to display more aggressive features, such as larger tumor size, poor differentiation, positive lymph nodes, high proliferation rates, higher incidence of Human Epidermal Growth Factor Receptor 2 (HER2/neu) over-expression, abnormal p53 expression, DNA aneuploidy, estrogen receptor/progesterone receptor negativity, and more tumors of the basal-like histologic subtype (3-10).

Studies dating back over thirty years have reported a high proportion of “rapidly progressing breast cancer” (RPBC) with inflammatory BC (IBC) characteristics in the North African country of Tunisia (11-13). A recent study of a retrospective series of Tunisian IBC cases classified according to the International Union Against Cancer T4d classification found these IBC cases presented at younger ages than both Tunisian non-IBC cases, and IBC cases in Europe and the US (14). A small case series (n=48) of invasive BCs among Tunisian women less than thirty years of age found that nearly all BCs associated with pregnancy or lactation were RPBCs (15), while another earlier

Tunisian study reported 79% of pregnancy associated BCs (n=52) were RPBC (12). Findings from these Tunisian studies have spurred interest in further BC research in the mid-East, and particularly in North Africa. Recent BC studies in the region have focused on Egypt, aided by the founding of the Gharbiah population-based cancer registry (GCR) in 1998 as part of the Middle East Cancer Consortium (MECC) (16).

Multiple studies have suggested an increased proportion and/or incidence of a younger-onset BC type in North Africa as compared to other regions, and that younger onset cancers may be of different etiology, carry different risk factor profiles, and have worse prognostic characteristics than those occurring later in life. However, no studies have examined younger onset BCs in a population based cancer registry in a North African country (1-15). Therefore, this study compared BC cases in the GCR to those in the US Surveillance, Epidemiology, and End Results (SEER) database, stratified by age. Between-country differences for younger and later onset BCs may indicate different etiologies and have important implications for public health BC prevention efforts and clinical practice.

Materials and methods

Data Sources

Data sources for this study include the GCR in Tanta, Egypt, and the US SEER database. The GCR is based 90 Km north of Cairo in the Nile Delta region. The GCR is a population-based registry covering the Gharbiah Governorate of Egypt. The registry was established in 1998 within the US National Cancer Institute sponsored MECC joint cancer registration project, with case registration beginning in 1999. The GCR is jointly sponsored by MECC and the Egyptian Ministry of Health and Population based in Cairo,

and is housed in the Tanta Cancer Center. Medical doctors affiliated with the Tanta Cancer Center conduct active surveillance for all incident cancer cases among the approximately 3.4 million residents of Gharbiah diagnosed within and outside the governorate. Data is gathered through regular visits to all government, non-government, and private centers and laboratories which treat cancer patients. Data collectors regularly visit and collect data from centers outside Gharbiah for residents of the governorate who are diagnosed or treated in other neighboring governorates or at the National Cancer Institute in Cairo. Data are also collected from the death certificates and the electronic mortality database of the governorate. While case reporting is not required by law, a ministerial decree issued to request collaboration with the registry has aided data collection efforts (16). The GCR data is subjected to routine quality control and validation and has been included in publications of the US National Cancer Institute (MECC reports) and the Cancer Incidence in Five Continents monograph of the International Agency for Research on Cancer (16-18).

The other data source for this paper was the SEER 18 Registries database. The dataset includes all BC cases from 2000 forward for the following SEER registries: San Francisco-Oakland, Connecticut, Detroit (metropolitan area), Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta (metropolitan area), San Jose-Monterey, Los Angeles, Alaska Natives, rural Georgia, California excluding San Francisco/San Jose-Monterey/Los Angeles, Kentucky, Louisiana, New Jersey, and greater Georgia (19).

Data Management and Statistical Analysis

Variables of interest that were available in both datasets included age at diagnosis (continuous), tumor grade, International Classification of Diseases for Oncology-3 (ICD-O-3) histology (20), estrogen and/or progesterone receptor overexpression (positive vs. negative), and American Joint Committee on Cancer (AJCC) stage group (21). ICD-O-3 histology codes examined included mucinous (8480, 8481); duct, not otherwise specified (NOS; 8500); medullary (8510, 8512, 8513); lobular, NOS (8520); duct and lobular (8522); Paget Disease, mammary (8540, 8541, 8543); and sarcomas, including Phyllodes tumor (8935-8982, 9020). Due to an extremely small number of cases in the GCR (each less than 1% of total cases), papillary (8050, 8260, 8503), tubular (8211), inflammatory (8530), duct mixed with other carcinoma types (8523), and lobular mixed with other carcinoma types (8524) were grouped into an “other” category along with all other histologies (20). AJCC 6th edition staging information was available in each dataset for the years 2004 to 2008. This analysis therefore includes all adult (18+ years of age) malignant female breast cancer cases diagnosed from 2004 to 2008 (excluding in-situ/Stage 0 cases and lymphomas).

GCR BC cases were compared to US SEER BC cases on each variable of interest initially through standard bivariate analysis. An independent group t-test was used to determine if there was a statistically significant difference between the mean ages of each population, while potential differences in all other variables, which were categorical, were tested using Pearson’s chi-square statistic. A logistic regression model was fit to examine the multivariate association between country of residence and tumor characteristics, with the general model outlined below:

$\text{Logit}(p) = \beta_0 + \beta_1(\text{age}) + \beta_2(\text{hormone receptor status}) + \beta_3(\text{grade}) + \beta_4(\text{histology}) + \beta_5(\text{stage})$

where $\text{logit}(p)$ is the log odds of an Egyptian BC (vs. one from the US). For modeling purposes, hormone receptor status was considered positive if a case was estrogen and/or progesterone receptor positive and negative if a case did not test positive for either of these hormone receptors, grade was categorized as low grade I/II vs. high grade III/IV, histology as ductal, NOS vs. other, and stage was grouped into four categories fit as indicator variables (I/referent, II, III, IV) based on AJCC stage group. All tests were two-tailed with an alpha level of 0.05.

In order to examine potential heterogeneity in tumor characteristics by age between the two countries and to account for age differences between the two populations, between country differences were also examined within each of three age categories: ≤ 40 years of age (very young onset; likely pre-menopausal), 41-55 years of age (younger onset; pre/peri/post-menopausal) and ≥ 56 years (likely post-menopausal onset). In addition, age stratified incidence rates for each tumor characteristic were also calculated using yearly (2004-2008) population denominator estimates from the US and Egyptian census programs. Due to the structure of the Egyptian population denominator estimates, age categories were slightly modified to 25-39, 40-54, ≥ 55 years of age for the purposes of incidence rate calculations. Incidence rates were calculated using SEER*stat version 7.1.0 (National Cancer Institute, Bethesda, MD) and OpenEpi version 2.3.1

(Emory University, Atlanta, GA); all other analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC).

Results

This analysis included 3,819 cases from the GCR and 273,019 from SEER. Four GCR cases were missing age at diagnosis and have been excluded from all analyses. No cases were missing histology. Grade information was missing for 1,029 GCR and 25,463 SEER cases. Complete hormone receptor information was missing for 1,886 GCR and 24,788 SEER cases, while 792 GCR and 18,221 SEER cases were missing complete stage information. However, 9 GCR and 609 SEER cases were able to be assigned to an overall stage 3, and were included in the logistic regression models. Cases missing information for a particular variable were excluded from analyses involving that variable.

Table 4.1 shows the GCR and SEER population characteristics for all ages combined and for cases ≤ 40 years of age, along with the p-value derived from test statistics comparing the two populations on each variable. GCR and SEER cases differed significantly in age, grade, hormone receptor status, histology, and stage. The average age of GCR cases was ten years younger than that of SEER cases (51.0 vs. 61.4 years). The majority (88%) of GCR cases, including those ≤ 40 years of age, were diagnosed with grade II, or moderately differentiated tumors. However, the majority (56%) of younger (≤ 40 years of age) SEER cases were diagnosed with grade III, poorly differentiated tumors. Younger GCR and SEER cases also differed significantly on hormone receptor status, with 23% of GCR cases 40 years of age or younger being

hormone receptor negative vs. 33% of younger SEER cases. Histologies varied between the two populations, though for both the large majority were duct, NOS. Among rarer histologies, for all ages combined and among younger cases, the GCR had a higher percentage of medullary, mammary Paget disease, sarcomas, and “other”, while SEER had a higher percentage of mucinous, lobular NOS, and duct & lobular.

There was large, statistically significant variation in stage at diagnosis between the two populations. GCR cases were diagnosed at later stages, with less than 5% being diagnosed at Stage I and 12% being diagnosed at Stage IV. Forty-eight percent of SEER cases (all ages combined) were diagnosed at Stage I, although this dropped to 30% among those aged 40 and younger. Only 5-6% of SEER cases were diagnosed at Stage IV, even among those 40 years or younger. Cases aged 41-55 and those 56 and older followed a similar pattern to all ages combined with regard to differences in grade, hormone receptor status, histology, and stage ($p < 0.01$ for each; results not shown).

Table 4.2 shows the odds ratios (OR) and 95% confidence intervals (CI) obtained from age stratified logistic regression models examining the multivariate relationship between country of residence (Egypt’s GCR vs. US SEER) and BC characteristics. The first model combined all age groups, and found younger age at diagnosis (OR=0.95, 95% CI=0.94-0.95), lower grade I/II (OR=0.05, 95% CI=0.04-0.06), negative hormone receptor status (OR=1.95, 95% CI=1.72-2.22), greater stage: Stage II (OR=12.04, 95% CI=9.69-14.97), Stage III (OR=44.55, 95% CI=35.84-55.38), Stage IV (OR=16.04, 95% CI=11.97-21.50) vs. Stage I (referent), and duct, NOS histology (OR=4.30, 95% CI=3.5-5.07) were all independently associated with the GCR cases. The model examining cases ≤ 40 years of age generated similar results: OR for

high vs. low grade=0.04, 95% CI=0.02-0.06; negative vs. positive hormone receptor status OR=1.67, 95% CI=1.26-2.22; Stage II OR=10.57, 95% CI=5.84-19.13; Stage III OR=31.57, 95% CI=17.43-57.19; Stage IV OR=16.53, 95% CI=8.12-33.64 vs. Stage I referent, and duct, NOS vs. all other histologies OR=2.61, 95% CI=1.82-3.75. Cases aged 41-55 and those over 56 years of age followed a similar pattern (results shown in Table 4.2).

Table 4.3 gives the country- and age-specific incidence rates per 100,000 woman-years and 95% CI for tumor grade, hormone receptor status, histology, and AJCC stage. Incidence rates for the US SEER were generally higher with a few exceptions. Egyptian women <40 years of age had a higher incidence of low grade I/II tumors (17.4 vs. 11.9). Egyptian GCR cases had higher rates of Stage III and IV cancers across all age groups with the exception of stage IV cancers among women aged 55 and older.

Discussion

The results of this study reveal significant differences in age, tumor grade, hormone receptor status, histology, and stage between the BC cases included in Egypt's GCR and the US SEER registries. Egyptian GCR cases were, on average, over 10 years younger than US SEER cases, with nearly 19% of GCR cases \leq 40 years of age as compared to only 6% of US SEER cases. Although there are age differences in the underlying population structure of the two countries, we have accounted for these differences by conducting an age-stratified analysis based on clinically and biologically relevant cut-points, as well as adjusting for age in the model that included all age groups combined (22, 23). However, the possibility of residual confounding still exists.

As noted earlier, younger onset cases tend to have worse prognostic characteristics (3-10). Furthermore, BC risk factors such as age at menarche, age at first full term birth (FFTB), parity, obesity, and oral contraceptive (OC) use have all been shown to demonstrate quantitative and qualitative age interactions with regard to BC risk (24, 25). A review of 26 published manuscripts concluded early age at menarche and later age at FFTB increase the risk of premenopausal more than postmenopausal BC risk (26), while Anderson et al. found age at menarche and FFTB interacted quantitatively, but not qualitatively with age (24). Nulliparity has been shown to decrease the risk of early onset BCs, but increase the risk of BC in older women (24). Body mass index (BMI) also qualitatively interacts with age in regard to BC risk. Higher BMI has been shown to have an inverse relationship with premenopausal BC risk, but a positive relationship with postmenopausal BC risk (25). In a Polish case-control study, Anderson et al. also observed a qualitative interaction between OC use and age, where OC ever-use was associated with decreased BC risk for women less than 40-44 years old, after which the risk was elevated for OC ever-users (24).

Although we know average age at menopause is younger in Egyptian women as compared to the US (46.7 vs. 51 years in the US), this likely does not explain the differences seen in cases ≤ 40 years of age (27, 28). Nationally representative surveys in each country and recently published studies have shown that Egyptian women, on average, have a slightly older age at menarche, have more children and have them at a younger age, are less likely to use oral contraceptives, but have a slightly higher prevalence of obesity than US women (29-34). Unfortunately, information on BC risk

factors for individual cases was not available in either database for examination in this study.

A high proportion of GCR cases, including those ≤ 40 years of age (88%), were assigned a tumor grade of II, moderately differentiated, as compared to SEER cases, where only 42% of all cases were grade II. This was also reflected in the incidence rates for tumor grade in this age group. However, among SEER cases ≤ 40 years of age, the majority (56%) were found to have grade III, poorly differentiated tumors, indicating these tumors may be more aggressive than those found in older women. It is unclear why there is such a large variation in grade between the two countries. The GCR and SEER program use virtually identical rules for recording tumor grade, so it is unlikely coding differences would be the sole explanation for grade differences between the registries (35-37).

Grade II tumors have been shown to have the lowest concordance in reliability studies, as opposed to grade I and III tumors where misassignment of one to the other is rare. It is likely that many tumors on the border of being either grade I or III are up coded or down coded to grade II, thus increasing the proportion of grade II tumors. Furthermore, tissue sampling, handling, preservation, fixation, and preparation can all affect the accuracy and reliability of grade determination (38). In addition, as neither registry program has a central laboratory for tissue examination, differences in accuracy, reliability, and general laboratory quality both between the GCR and SEER registries as well as institutions contributing cases to each registry are to be expected. However, a recent study examining molecular subtypes of BC in archival tissue samples from the

Universities of Cairo and Minia in Egypt also found over 80% of tumors were classified as grade II using Nottingham criteria, which might suggest better prognosis (39).

While a larger percentage of SEER cases ≤ 40 were hormone receptor negative as compared to GCR cases of the same age (33% vs. 23%), in multivariate logistic regression models, the odds of GCR BC cases being hormone receptor negative were greater as compared to SEER cases across all age groups. Our results for estrogen and progesterone receptor status separately (not shown) are similar to those in the recent Egyptian case series by Salhia et al., where over all ages combined, 65% of tumors were found to be estrogen receptor positive and 44% progesterone receptor positive (39). Another study using GCR data from 2001-2006 also found the incidence of hormone receptor positive BC was higher than negative (40).

Interestingly, the percent of hormone receptor negative BC remained relatively flat across all age groups in the GCR data (approximately 22-23%), whereas in the US SEER data, the percent of hormone receptor negative cancers went from a high of 33% among women ≤ 40 years of age down to only 18% among women aged 56 years and older. It is unclear if this represents underlying etiologic or genetic differences between the two populations, or if this represents a type of cohort effect due to major changes in the lifestyle, reproductive, and environmental exposures Egyptian women have experienced in the past few decades, namely the modernization the country has undergone leading to an increase in exposure to the “western” lifestyle. This is especially true of adult weight-gain and post-menopausal obesity, which have been found to be associated with the incidence of hormone receptor positive BC in multiple epidemiologic studies (41-43). Recent estimates of obesity prevalence among Egyptian women are close to

40%, which is higher than recent estimates for US women (31, 34). If these trends continue, it is possible Egyptian post-menopausal BC rates may eventually equal those in the US.

It should be noted that hormone receptor status testing is not necessarily routine practice in Egypt, and in fact, only 51% of GCR cases had complete hormone receptor information available in this analysis, as opposed to 91% of US cases (39). However, due to an increase in hormone receptor testing in recent years in Egypt, this represents a higher proportion of cases with this information than our previous study (40). We conducted a sensitivity analysis in order to aid in determining what effect, if any, GCR cases missing hormone receptor status had on the results. GCR cases missing hormone receptor status were on average one year older, although there was no significant difference between those missing and not missing hormone receptor status by the three age categories. GCR cases missing hormone receptor status were also more likely to be diagnosed with duct & lobular, mammary Paget disease, sarcomas, and “other” histologies, although as sarcomas are not amenable to hormonal treatment, it makes sense cases with these cancers may not necessarily be tested for hormone receptors. Those missing hormone receptor information were also more likely to be diagnosed with undifferentiated/anaplastic/Grade IV and stage IV cancers, so it is possible women with more advanced cancers were not tested for hormone receptor status. However, when the models were re-run with those cases missing hormone receptor status (i.e., excluding hormone receptor status as a covariate), the results were similar to those presented in Table 2.2, indicating excluding those missing hormone receptor status did not have a strong effect on the overall model estimates.

In multivariate models, Egyptian GCR cases were more likely to be diagnosed with duct, NOS BC as compared to the US SEER cases across all ages. Invasive ductal carcinoma is the most common type of BC, and prognosis is dependent on factors such as grade, hormone receptor status, and stage at diagnosis (44). Among rarer histologies, the GCR had a higher percentage of medullary, mammary Paget disease, sarcomas, and “other”, while SEER had a higher percentage of mucinous, lobular NOS, and duct & lobular.

Mucinous carcinomas tend to occur in older women, have less chance of spreading to the lymph nodes, are more likely to be estrogen receptor positive and HER2/neu negative, and generally carry a better prognosis, while lobular carcinomas have a similar prognosis to invasive ductal carcinomas (44, 45). Medullary carcinomas are more common among younger women and those with a *BRCA1* mutation. Although it is currently unknown if the medullary subtype carries a better or worse prognosis than other more common BC histologies, they are more commonly estrogen receptor negative (45). Mammary Paget disease most often presents as a persistent, scaling, eczematous, or ulcerated lesion involving the nipple/areola, and is often misdiagnosed as either eczema or psoriasis. It is almost always an extension of an underlying breast adenocarcinoma that may be present even where breast examination and mammogram results are normal (46). Prognosis varies with stage at diagnosis, although those presenting with a mass at diagnosis often have more advanced cancer (45). Breast sarcomas tend to have a poorer prognosis, with outcome being more dependent on tumor size as opposed to grade (47, 48). Malignant Phyllodes tumors contain stromal and glandular tissue, and tend to occur in women in their thirties or forties (49). Their clinical

course, treatment, and survival rates are similar to other pure breast sarcomas (47, 49). Breast sarcomas and Phyllodes tumors differ from other BC in that they do not respond to hormone therapy, and are less likely to respond to chemotherapies and radiation treatment used for other BC types (49).

Unlike previous reports from North Africa, inflammatory BC (IBC) constituted a very small proportion of total cases in the GCR (11-13, 50). IBC is primarily a clinical diagnosis based largely on the classic presentation of rapid onset of erythema, edema, and peau d'orange appearance of the breast (51). Therefore, relying solely on ICD-O-3 histology likely underestimates the incidence of IBC (51-54). Soliman et al. applied a simplified clinical definition classifying BC cases as most-likely IBC, possibly IBC, and non-IBC depending on the presence of erythema, edema, and peau d'orange (most-likely IBC), two of the three symptoms or peau d'orange only (possible IBC), or edema only, erythema only, or none of the three symptoms (non-IBC) to GCR BC cases diagnosed between 1999 and 2003 (55). This study reported 11.1% of BC cases in the GCR were most likely or possible IBC cases (55). If all these cases were to be considered true IBC, this would be a much higher percentage than the recently reported 1.9% using a comprehensive case definition applied to US SEER data (51). Unfortunately, information regarding IBC clinical symptoms was not available in the GCR for the more recent years examined.

One of the most striking results was that after adjustment for age, grade, hormone receptor status, and histology, GCR cases were nearly 45 times more likely to be diagnosed at stage III and 16 times more likely to be diagnosed at stage IV than US SEER cases, with similar results across all age groups in age stratified analysis.

Furthermore, this finding was also reflected in the country- and age-stratified incidence rates by stage, where the incidence of stage III and IV cancers was higher in the Egyptian GCR regardless of age (with the exception of stage IV BC among women over 55 years of age). Although it has been previously reported that Egyptian cases present with advanced disease, this is the first study to our knowledge to directly compare US to Egyptian BC cases on AJCC stage groups while adjusting for other established prognostic factors (39). While it is possible that some unknown/unadjusted for tumor characteristic(s) exists that differs between these two populations and causes more aggressive disease in Egyptian women, a more likely explanation is that Egyptian women do not have their BC diagnosed as early in the disease process as US women. If this is in fact the case, this finding represents a modifiable prognostic factor amenable to readily available educational and clinical interventions. Educating Egyptian women on the signs and symptoms of BC and encouraging them to seek health care when any are noticed represents a relatively easy and low cost way to intervene earlier in the disease process, when surgery, hormonal and chemotherapy, and radiation treatment are most efficacious. Increasing the availability of regular mammography screening to Egyptian women where resources are available to do so may also lead to diagnosis of BC at earlier stages in this population (39).

In conclusion, Egyptian GCR and US SEER cases significantly differ in age at diagnosis, tumor grade, hormone receptor status, histology, and stage, with these differences in tumor characteristics persisting in age stratified and multivariate analysis. As detailed BC risk factor information was not available in either registry, it is unclear what factors are leading to the differences in age at diagnosis, tumor grade, hormone

receptor status, and histology. There has been a recent and relatively large increase in the prevalence of obesity in Egypt, which represents a modifiable BC risk factor and area for future research in Egypt and other middle-income countries that now grapple with an increasing chronic disease burden traditionally associated with “western” lifestyle factors (56). Egyptian GCR cases were much more likely to be diagnosed at later stages, and this prognostic factor is amenable to currently existing educational interventions and screenings. Future research should examine currently recognized as well as novel genetic and environmental factors that may contribute to the tumor characteristic differences between these two populations, as well as examining how these differences may contribute to treatment and survival differences.

Table 4.1 Characteristics of Gharbiah, Egypt and US SEER Breast Cancer Cases, 2004-2008

	Gharbiah Cancer Registry n and (%)		US SEER Registries n and (%)		P-Value	
Mean Age at Diagnosis (SD)	51.0 (11.5)		61.4 (14.3)		<0.0001 ^a	
Age in Years					<0.0001 ^b	
≤ 40	713 (18.7)		17,199 (6.3)			
41-54	1,842 (48.2)		84,122 (30.8)			
≥ 55	1,264 (33.1)		171,698 (62.9)			
	All Ages Combined	≤ 40 years of age	All Ages Combined	≤ 40 years of age	All Ages Combined	≤ 40 years of age
Grade					<0.0001 ^b	
I	29 (1.0)	5 (0.9)	53,146 (21.5)	1,362 (8.6)		
II	2465 (88.4)	472 (88.2)	104,147 (42.1)	5,252 (33.0)		
III	241 (8.6)	49 (9.2)	86,815 (35.1)	8,945 (56.2)		
IV	55 (2.0)	9 (1.7)	3,448 (1.4)	369 (2.3)		
Missing (% of Total Cases)	1029 (26.9)	178 (25.0)	25,463 (9.3)	1271 (7.3)		
Hormone Receptor					0.02 ^b	
Positive	1495 (77.3)	278 (77.4)	197,482 (79.6)	10,583 (66.9)	<0.0001 ^b	
Negative	438 (22.7)	81 (22.6)	50,749 (20.4)	5,233 (33.1)		
Missing (% of Total Cases)	1886 (49.4)	354 (49.6)	24,788 (9.1)	1383 (8.0)		
Histology ^c					<0.0001 ^b	
Mucinous	36 (0.9)	6 (0.8)	6,430 (2.4)	259 (1.5)	<0.0001 ^b	
Duct, NOS	2,812 (73.6)	530 (74.3)	191,138 (70.0)	13,652 (79.4)		
Medullary	56 (1.5)	17 (2.4)	1,283 (0.5)	196 (1.1)		
Lobular	155 (4.1)	14 (2.0)	22,155 (8.1)	495 (2.9)		
Duct & Lobular	57 (1.5)	22 (3.1)	19,992 (7.3)	892 (5.2)		
Paget Disease, Mammary	43 (1.1)	14 (2.0)	1,003 (0.4)	99 (0.6)		
Sarcomas; Phyllodes Tumor	46 (1.2)	14 (2.0)	703 (0.3)	127 (0.7)		
Other	614 (16.1)	96 (13.5)	30,315 (11.1)	1,479 (8.6)		
AJCC Stage Group					<0.0001 ^b	
I	144 (4.7)	22 (3.9)	122,936 (48.1)	4,887 (30.1)	<0.0001 ^b	
IIA	632 (20.8)	108 (19.4)	60,856 (23.8)	4,643 (28.6)		
IIB	546 (18.0)	113 (20.3)	25,909 (10.1)	2,627 (16.2)		
IIIA	701 (23.1)	135 (24.2)	17,205 (6.7)	1,910 (11.8)		
IIIB	188 (6.2)	29 (5.2)	6,190 (2.4)	436 (2.7)		
IIIC	444 (14.6)	87 (15.6)	7,914 (3.1)	777 (4.8)		
IV	372 (12.3)	64 (11.5)	13,788 (5.4)	937 (5.8)		
Missing (% of Total Cases)	792 (20.7)	155 (21.7)	18,221 (6.7)	982 (5.7)		

^aBased on t-test comparing Egyptian and US breast cancer cases, missing not included^bBased on chi-square test comparing Egyptian and US breast cancer cases, missing not included^cNo cases missing histology

Table 4.2 Odds Ratios and 95% Confidence Intervals from Age Stratified Logistic Regression Models Examining the Relationship between Country of Residence and Breast Cancer Characteristics, Egypt's GCR and US SEER cases, 2004-2008^a

Variable	Odds Ratio (95% Confidence Interval)			
	Model 1: All Ages Combined	Model 2: ≤ 40 Years of Age	Model 3: 41-55 Years of Age	Model 4: ≥ 56 Years of Age
Age (continuous)	0.95 (0.94-0.95)	-	-	
Grade				
Low (I/II) ^b	1.00	1.00	1.00	1.00
High (III/IV)	0.05 (0.04-0.06)	0.04 (0.02-0.06)	0.05 (0.04-0.06)	0.07 (0.05-0.10)
Hormone Receptor				
Positive ^b	1.00	1.00	1.00	1.00
Negative	1.95 (1.72-2.22)	1.67 (1.26-2.22)	2.19 (1.83-2.62)	1.87 (1.50-2.33)
Histology				
Other ^b	1.00	1.00	1.00	1.00
Duct, NOS	4.30 (3.65-5.07)	2.61 (1.82-3.75)	4.62 (3.64-5.88)	5.37 (4.02-7.19)
AJCC Stage Group				
I ^b	1.00	1.00	1.00	1.00
II	12.04 (9.69-14.97)	10.57 (5.84-19.13)	10.99 (8.14-14.85)	14.93 (10.29-21.65)
III	44.55 (35.84-55.38)	31.57 (17.43-57.19)	40.96 (30.35-55.28)	64.68 (44.65-93.70)
IV	16.04 (11.97-21.50)	16.53 (8.12-33.64)	11.87 (7.56-18.64)	21.23 (13.16-34.28)

^aAll variables in each column are mutually adjusted for each other

^bReferent Category

Table 4.3 Age Stratified Average Incidence Rates by Country of Residence and Breast Cancer Characteristics, Egypt's GCR and US SEER cases, 2004-2008

Variable	Incidence Rate per 100,000 Woman-Years (95% Confidence Interval)					
	25-39 Years of Age		40-54 Years of Age		≥ 55 Years of Age	
Registry	Egypt's GCR	US SEER	Egypt's GCR	US SEER	Egypt's GCR	US SEER
Grade						
Low (I/II)	17.4 (15.7-19.2)	11.9 (11.6-12.3)	76.5 (72.3-80.9)	95.2 (94.3-96.1)	91.2 (85.3-97.4)	221.4 (220.1-222.7)
High (III/IV)	2.3 (1.7-3.0)	17.9 (17.5-18.3)	8.2 (6.9-9.7)	68.5 (67.7-69.3)	11.8 (9.7-14.1)	104.7 (103.8-105.6)
Hormone Receptor						
Positive	10.3 (9.0-11.7)	19.4 (19.0-19.8)	45.2 (42.0-48.5)	125.9 (124.9-127.0)	56.4 (51.8-61.3)	268.3 (266.8-269.7)
Negative	2.8 (2.1-3.5)	10.2 (9.9-10.5)	13.8 (12.1-15.7)	38.4 (37.9-39.0)	16.0 (13.6-18.7)	58.9 (58.2-59.6)
Histology						
Other	6.3 (5.3-7.4)	6.6 (6.3-6.8)	29.8 (27.2-32.6)	47.6 (47.0-48.3)	40.5 (36.6-44.7)	117.7 (116.7-118.6)
Duct, NOS	19.5 (17.7-21.4)	25.6 (25.1-26.1)	84.1 (79.8-88.7)	130.0 (128.9-131.0)	107.0 (100.6-113.7)	245.9 (244.5-247.3)
AJCC Stage Group						
I	0.9 (0.6-1.4)	8.6 (8.4-8.9)	4.6 (3.6-5.7)	73.0 (72.2-73.8)	5.3 (3.9-6.9)	174.9 (173.7-176.1)
II	7.5 (6.4-8.7)	13.8 (13.4-14.1)	37.7 (34.8-40.8)	63.6 (62.8-64.3)	42.2 (38.2-46.5)	105.4 (104.5-106.3)
III	9.8 (8.6-11.2)	6.1 (5.9-6.3)	40.3 (37.3-43.5)	24.4 (24.0-24.9)	49.6 (45.2-54.2)	36.9 (36.4-37.5)
IV	2.4 (1.8-3.1)	1.8 (1.7-2.0)	9.2 (7.8-10.8)	7.5 (7.2-7.7)	18.0 (15.4-20.8)	19.5 (19.1-19.9)
Total	25.7 (23.7-27.9)	32.2 (31.7-32.7)	113.9 (108.8-119.2)	177.6 (176.4-178.8)	147.5 (139.9-155.4)	363.5 (361.8-365.2)

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Chapter 5

Conclusions

Summary of Findings

Although there is a large body of literature on the epidemiology of breast cancer (BC), there is still little known regarding rarer types of BC. This dissertation expands upon the inflammatory BC (IBC), young-onset, and Egyptian BC literature by examining IBC incidence and survival in the United States (US) by socioeconomic position (SEP), race/ethnicity, and age, as well as examining differences between US and Egyptian BC stratified by age.

Unlike overall BC in the US, this dissertation found incidence rates for IBC increased as county-level SEP decreased. Low SEP was found to be associated with higher odds of IBC even after adjustment for race/ethnicity and age at diagnosis (1). Kaplan-Meier survival curves showed stage III IBC cases residing in low SEP counties had lower median survival than both IBC cases residing in higher SEP counties as well as non-IBC cases regardless of their county-level SEP. In multivariate proportional hazards models, residing in a low SEP, non-metropolitan county was associated with a significantly greater hazard of death for non-IBC cases (2). In multivariate analyses, African Americans were shown to have a higher incidence of IBC and lower survival (1, 2). Finally, Egyptian and US cases significantly differed in tumor grade, hormone receptor status, and histology across all age groups. Most notably, Egyptian cases were

much more likely to be diagnosed at a later stage than their US counterparts, even after adjustment for age, grade, hormone receptor status, and histology.

Strengths and Limitations

The major strengths of this dissertation include addressing research questions with important clinical and public health implications for two rare and deadly types of BC (IBC and young-onset BC), for which little epidemiologic data exist, as well as use of the large and high quality US Surveillance, Epidemiology, and End Results (SEER) database and the only US National Cancer Institute (NCI) sponsored population-based registry in Egypt, the Gharbiah Regional Cancer Registry (GCR). The US SEER registries cover approximately 28% of the US population, including 26% of African Americans, 41% of Hispanics, 32 % of American Indians and Alaska Natives, 54% of Asians, and 71% of Native Hawaiian/Pacific Islanders (3). Furthermore, the SEER program is considered the standard for cancer registry data quality worldwide. Quality control studies, including case-finding, recoding, and reliability studies are continually conducted by the SEER program to ensure the data included in the registries is accurate and collected and recorded in a uniform and timely manner across all registries (4).

The GCR is a population-based registry covering the Gharbiah Governorate of Egypt. The registry was established in 1998 within the US NCI sponsored Middle East Cancer Consortium (MECC) joint cancer registration project, with case registration beginning in 1999. Medical doctors affiliated with the Tanta Cancer Center conduct active surveillance for all incident cancer cases among the approximately 3.4 million residents of Gharbiah diagnosed within and outside the governorate (5). BC case

abstraction and variable coding is similar to that used by the SEER program (6-8). GCR data are subjected to reliability and accuracy assessments, including both internal and external record abstraction validation as well as external assessment of case ascertainment, data completeness, and accuracy. Use of CANREG software developed by the International Agency for Research on Cancer (IARC) as well as staff participation in a standardized training course also help ensure the reliability and accuracy of the data recorded by the GCR (9). Furthermore, the GCR is included in the IARC monograph *Cancer Incidence in Five Continents, Volume IX*, with IARC requiring >80% of all cancer cases to be microscopically verified, <10% registered from a death certificate only, and <10% with an unknown basis of diagnosis (10).

While these studies use data sources considered to be of high quality, and the results of these analyses have important clinical and public health implications that are detailed in the next section, there are several limitations that should be noted. Though SEER data are broadly representative of the US population, there are a few differences. Cases recorded in the SEER database are more likely to be foreign born and urban as compared to the US population as measured in the 2000 census (11). However, due to the US SEER's large size and over 30 years of follow-up, it is generally considered to accurately represent the overall US cancer population (11).

With regard to the GCR, as reporting is not required by law, there may be issues with under-ascertainment of BC cases, especially among elderly rural populations (10). The GCR also has significantly fewer years of follow-up compared to the US SEER as case registration did not begin until 1999. However, GCR staff employ active surveillance both within and outside Gharbiah to help ensure all cases residing within the

governorate are recorded (5). Furthermore, the GCR offers a unique opportunity to study cancer in Egypt in the context of a population-based registry.

Another limitation to both registries is lack of individual level BC risk factor information, as well as information on Human Epidermal Growth Factor Receptor 2 (HER2/neu) for the years evaluated. HER2/neu overexpression/amplification has emerged as an important prognostic factor and clinically relevant marker due to the availability of targeted therapies such as trastuzumab. Although budgetary, time, and privacy constraints make BC risk factor collection on a registry wide basis unlikely, both registries have recently begun to collect data on HER2/neu status (12, 13).

Future Research and Public Health Implications

These studies point to a disparity in the incidence and survival from IBC in the US as well as between Egyptian and US BC cases on important prognostic factors, notably stage at diagnosis. In the US, African American women and those residing in lower SEP counties have a higher incidence of IBC, contrary to the large body of literature showing lower overall BC incidence in these groups. Analytic studies of IBC are needed to determine why this disparity exists, with special emphasis on well-established reproductive and lifestyle-related BC risk factors that may not behave in the same way with regard to IBC risk. Novel genetic and environmental IBC risk factors should also be explored. Furthermore, both IBC and non-IBC survival was found to be lower among lower SEP county dwellers and African Americans. This finding points to the need to direct BC education and screening programs to these traditionally underserved groups, with special focus on IBC symptoms and detection as these are not

generally addressed in BC public education campaigns. Finally, relatively low-cost educational programs advising Egyptian women on breast self-awareness, BC signs and symptoms, and when to seek medical attention, as well as increasing access to regular mammography screening where feasible would likely lead to earlier stage at diagnosis as has been seen in the US and other developed countries.

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