Differences in Inflammatory Breast Cancer Characteristics and Outcomes Between Caucasian and Hispanic Women in the US

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Differences in Inflammatory Breast Cancer Characteristics and Outcomes Between Caucasian and Hispanic Women in the US

Aruna Chung-A-Hing

A Thesis in the Field of Biology
for the Degree of Master of Liberal Arts in Extension Studies

Harvard University
November 2018
Abstract

Mortality from breast cancer has declined over time in the US, but breast cancer remains the second leading cause of cancer death among women overall and the leading cause of cancer death among Hispanic women. In the US, the proportion of inflammatory breast cancer cases ranges from 2% to 7%. Although inflammatory breast cancer (IBC) is considered to be the most aggressive form of breast cancer, only a small number of studies have attempted to analyze the characteristics and outcomes of inflammatory breast cancer among Hispanic Americans. Comparisons between racial and ethnic groups can propose different approach for research in cancer etiology, prevention, and outcomes and are necessary for determining inconsistencies in healthcare.

The goal of this research was to use the Surveillance, Epidemiology, and End Results (SEER) database to evaluating racial disparities in IBC occurrence between Caucasian women and Hispanic women living in the US. I used SEER*Stat to compare the clinicopathologic characteristics and outcomes of Hispanic and Caucasian women between the ages of 20 and 79 years old who were diagnosed between 1992 and 2014.

Age at diagnosis was similarly distributed between the two races until 35 years of age where an increase in rate was seen in Caucasian women compared to Hispanic women. Hispanic women displayed a lower incidence rate of IBC compared to Caucasian women. Caucasian and Hispanic women showed no significant differences in 5-year survival. Hispanic women also displayed a lower incidence rate of ER+ tumors compared to Caucasian. Caucasian women had higher incidence rate of PR+ tumors compared to Hispanic women. Understanding the
epidemiology of IBC by race may produce hypotheses about risk factors for IBC. Future investigation should focus on etiologic agents that may explain these differences.
Acknowledgments

Firstly, I would like to express my sincere gratitude to my thesis director Dr. Pagona Lagiou of the Department of Epidemiology at the Harvard School of Public Health. Thank you not only for the invaluable comments, patience, and encouragement but also for the hard questions which helped me to better my analysis.

I would also like to thank my research advisor Dr. James Morris for his guidance during the proposal and thesis writing process. Thank you for always being available to answer any questions, for the advice, and the support.

Finally, I must express my gratitude to my parents and sister for their support and motivation throughout my study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them.
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Breast Cancer

Breast cancer is the most frequently diagnosed cancer and among the leading causes of cancer death among females (Ban et al., 2014). Approximately 1.5 million women worldwide are diagnosed with breast cancer every year, many of whom will have disseminated tumor cells at first diagnosis. According to the Center for Disease Control, about 237,000 cases of breast cancer are diagnosed in women each year in the United States. And about 41,000 women in the U.S. die each year from breast cancer. Despite significant improvements in early diagnosis and treatment, these tumors will progress to clinically relevant and life-threatening lesions in about 20% of patients (Trent et al., 2005).

Due to significant improvements in screening, early diagnosis, and treatment in the recent decades, breast cancer mortality has decreased worldwide (Coleman et al., 2008). This leads to a situation where the total number of prevalent breast cancer cases is increasing, and therefore a growing number of women needing follow-up care (Lafranconi et al., 2017).

Inflammatory Breast Cancer

Inflammatory breast cancer is the most aggressive and lethal form of locally advanced breast cancer. Among women in the United States, it accounts for 6% of all breast cancer deaths. The prognosis for patients with IBC is poor, with only 32–42% surviving three years (Chang et
IBC is rare, where only 1% to 6% of all patients with breast cancer in the United States and the criteria for establishing the diagnosis are controversial (Bonnier et al., 1995).

Inflammatory breast cancer has been known by different names over the years, including mastitis carcinomatosa, acute mammary carcinoma, etc. Lee and Tannenbaum were the first to use the term "inflammatory breast cancer," and in 1924 provided a comprehensible clinical description of the malignancy (Lee and Tannenbaum, 1924). Patients with inflammatory breast cancer typically present with a sudden onset of increase in size of the breast, firmness, tenderness, ridging, thickening, warmness, and redness of the skin overlying the breast (Jaiyesimi et al., 1992). A study conducted in 1971 showed 57% of IBC patients have breast mass, 57% showed redness of the skin, 48% showed breast enlargement, 29% described pain in the breast or nipple, 16% had breast tenderness, 16% had generalized breast hardness, 13% had nipple retraction, 13% demonstrated edema of the skin, 9% had axillary mass, and 8% demonstrated warmness of the skin. Less commonly reported symptoms include axillary pain, itching of the nipple, swelling of the arm, and bone pain. The symptoms usually advance quickly, and most patients seek medical attention earlier than those with non-inflammatory breast carcinoma. The median duration of these symptoms before diagnosis was 2.5 months in the series reported by Haagensen compared with 5 months for non-inflammatory breast cancer (Haagensen, 1972).

Although very few studies have examined risk factors for IBC, it is seen to occur more often among younger than older women (Levine et al., 1985). Obese women may also have a greater risk of developing inflammatory breast cancer (Chang et al., 1998). Studies have shown
that rates for both black and white women nearly doubled from the mid-1970s to the early 1990s, and the pattern of better survival for white women compared with black women for all histologic types of breast cancer combined was also observed for IBC (Chang et al., 1998).

Race

Deaths from breast cancer have declined over time, but breast cancer remains the second leading cause of cancer death among women overall and the leading cause of cancer death among Hispanic women (Siegel et al., 2017). Inflammatory breast cancer has been shown to have a higher incidence rate among black women than white women (3.1 per 100,000 women-years for blacks compared to 2.2 for whites) (Hance et al., 2005). Further, overall survival has been reported to be significantly worse for blacks than whites (Chang et al., 1998). Although inflammatory breast cancer is considered to be the most aggressive form of breast cancer, a small number of studies have attempted to study the characteristics and outcomes of inflammatory breast cancer among Hispanic Americans. In the US, the proportion of IBC cases ranges from 1% to 6% of all breast cancer (Scott et al., 2017). Patients who are black or Hispanic have been reported to present with higher stage or more advanced non-inflammatory breast cancer (Patel et al., 2010).

A study done on tumor biologic factors and breast cancer prognosis among white, Hispanic, and black women in the United States revealed that, considering all stages, white women had the best overall survival (date of diagnosis to date of death) at 5 years, with a median survival of 166 months, but Hispanic women had an intermediate survival with median survival,
156 months (Elledge et al., 1994). Population-based studies of this very rare form of breast cancer are limited.

Hypothesis and Research Aims

I hypothesize that the incidence of inflammatory breast cancer will be lower and overall survival (date of diagnosis to date of death) will be higher among Caucasian women compared to Hispanic women in the US. My hypothesis is based on earlier studies that showed Caucasian women had the best overall five-year survival for non-inflammatory breast cancer survival of 75% ± 1% (median survival, 166 months), but Hispanic women had a five-year survival of 70% ± 2% (median, 156 months) for non-inflammatory breast cancer (Elledge et al., 1994)

I aim to compare the clinicopathologic characteristics and outcomes of Caucasian and Hispanic female inflammatory breast cancer patients residing in the US. The aim of this study is to advance our understanding of the burden of IBC in Hispanic populations by reporting the proportion of IBC among Hispanic women and Caucasian women from Surveillance, Epidemiology and End Results (SEER) registries [SEER 13 Regs Research Data, Nov 2016 Sub (1992-2014) <Katrina/ Rita Population Adjustment].

Thus, the primary purpose of this study is to reveal the population-based incidence of IBC. An additional goal is to evaluate changes in IBC incidence and survival over time, mainly by race. To examine these questions, I used a comprehensive definition designed to capture all of the clinically and pathologically defined IBC cases diagnosed in the National Cancer Institute’s SEER Program [SEER 13 Regs Research Data, Nov 2016 Sub (1992-2014) <Katrina/ Rita Population Adjustment].
To my knowledge, there have been no studies specifically examining the available demographic, clinicopathologic, and outcome-related inflammatory breast cancer parameters in the population-based Surveillance, Epidemiology, and End Results (SEER) database for the Hispanic American compared to the Caucasian American women. I aim to use the SEER database to compare the inflammatory breast cancer survival rates of Caucasians and Hispanic Americans living in the US to determine potential factors affecting differences in survival in these groups of women.

Research has revealed that breast cancer outcomes are improved when the disease is detected in its early stages. To direct programmatic and policy aid to those with the greatest need, there need to be incidence and mortality data to show which groups are most afflicted. This study will provide the opportunity to compare the clinicopathologic characteristics and outcomes of Caucasian and Hispanic female inflammatory breast cancer patients residing in the US. Understanding the determinants of IBC rates among different populations may help to design prevention strategies.
Chapter II
Materials and Methods

Ethical Statement

This study was based on public use de-identified data from the SEER database and did not involve interaction with human subjects or use personal identifying information. Informed patient consent was not required for the data published by the SEER database and I obtained Limited-Use Data Agreements from SEER. (Li et al., 2016)

SEER Database

The data for this study were derived from the Surveillance, Epidemiology and End Results (SEER) registries of the US National Cancer Institute. The SEER program of the National Cancer Institute (NCI) collects data on cancer diagnoses, treatment and survival for approximately 30% of the United States population. SEER presents incidence, survival and mortality data for histopathologic cancers and data by molecular subtyping. Data obtained for all primary invasive cancers include date of diagnosis age at diagnosis, gender, race/ethnicity, and county of residence and other demographic variables. The program registers the type of radiation therapy and whether delivery was neoadjuvant, adjuvant or intraoperative and data on chemotherapy use. SEER also collects tumor data on anatomic site, laterality for paired organs, size, and histopathological type. Cancer data are updated annually to obtain vital status, survival time, and cause of death. Follow up interval in SEER’s original 7 Tumor Registries now exceeds 40 years (Duggan et al., 2016).
The SEER program consists of 18 regional cancer registries with precise and consistent data collection and standards. The SEER program implements annual frequency distributions, incidence, prevalence and mortality rates over time on all cancers and site-specific cancers (Duggan et al., 2016). For this study SEER 13 Regs Research Data, Nov 2016 Sub (1992-2014) <Katrina/ Rita Population Adjustment> was used. SEER 13 covers approximately 13.4% of the U.S. population. Most years have expanded race/ethnicity rates/prevalence proportion and the rates/prevalence proportions are available by expanded race (white, black, American Indian/Alaska Native, and Asian or Pacific Islander) and Hispanic ethnicity (Hispanic and non-Hispanic). SEER cancer rates are age-adjusted within the populations at risk to the 2000 US standard population. Age standardization allows comparisons of cancer rates among different racial groups and geographic locations.

SEER provides data suitable for comparative analyses of cases within populations by defined characteristics, which allows it to answer crucial questions about racial variations. Age-adjusted incidence or mortality rates of cancer represent absolute risks of cancer, expressed as the number of newly diagnosed cancer cases or deaths per 100,000 persons per year. Cancer-specific survival analysis involves using only deaths identified as being due to a specified cancer as the outcome of interest. Patients who die of a cause other than the cancer under study are censored (Sarfati et al., 2010).

With its beginning in 1973, the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute coded IBC according to the International Classification of Diseases for Oncology 8530 designation, which required pathologic plugging of the dermal
lymphatics with tumor emboli (Duggan et al., 2016). Clinical inflammation is not considered for ICD-O 8530. The National Association of Central Cancer Registries (NAACCR) also has identified IBC cases by ICD-O 8530. Information on stage at diagnosis, tumor size, and ER/PR status in the nine oldest SEER cancer registries is available for cases diagnosed since 1975 for stage, since 1988 for tumor size, and since 1990 for ER/PR status (Hance et al., 2005).

Patient Selection

The study population consisted of all women diagnosed with inflammatory breast cancer from January 1, 1992, through December 31, 2014, in the SEER population-based cancer registries (SEER 13 Regs Research Data, Nov 2016 Sub (1992-2014) <Katrina/ Rita Population Adjustment>). Race/ethnicity was the primary exposure of interest, and Caucasian and Hispanic subjects residing in the US were selected utilizing the SEER*Stat algorithm. Women with other combinations of race/ethnicity were excluded from this study.

Study Variables

The inclusion criteria were as follow: female sex, Hispanic or Caucasian race/ethnicity, age of diagnosis between 20 and 79 years old, diagnosis between 1992 and 2014, pathologically confirmed infiltrating ductal carcinoma (inflammatory breast cancer) (SEER*Stat code: IDC, ICD-O-3 8500/3) as the primary and only cancer diagnosis, unilateral breast cancer, American Joint Committee on Cancer (AJCC) stage I to III, histological grades I to III, known tumor size, LN status, estrogen receptor (ER) and progesterone receptor (PR) statuses. The most widely used case description in the United States comes from the AJCC and is based on the original description of Haagensen. The AJCC defines IBC as a composite
A clinicopathologic entity characterized clinically by diffuse edema and erythema of the breast, over the majority of the breast and often without an underlying mass (Hance et al., 2005).

I examined histological grades by designating differentiation of malignant neoplasms where only malignant tumors are graded (Table 1). Differentiation details how much or how little a tumor matches the healthy tissue from which it originated. In general, the modifiers "well," "moderately," and "poorly" are used to indicate degrees of differentiation, which approximate to grades I, II, and III. Undifferentiated and anaplastic usually correspond to grade IV. When a diagnosis indicates two different degrees of grading or differentiation, the higher number is used as the grading code. The trend in breast cancer incidence rate was examined from 1992 through 2014 according to tumor size for three categories: 0 cm to 2 cm, 2.1 to 5.0 cm, and more than 5 cm, utilizing previously published groupings for evaluating the significance of early detection and mammography use (Chu et al., 1996).

Age of diagnosis between 20 and 79 years old women was selected for two reasons: (i) the rarity of breast cancer among women under age 20 years and (ii) the low levels of mammographic screening among women ≥80 years of age, which could influence the analysis of stage at diagnosis. 1992 was selected as the study starting point, because it was the first year that SEER started collecting information on Hispanic ethnicity. Additionally, patients diagnosed with breast cancer after 2014 will not be included to ensure an adequate follow-up duration as constructed by previous studies (Chen et al., 2015). Women who were diagnosed with breast cancer at death or by autopsy only and those with other first primary cancers, in situ disease, histological grade IV (undifferentiated or anaplastic), and no report of surgery or radiation
therapy were excluded from this study. IBC cases were identified using comprehensive SEER*stat code ICD-O 8530, which requires pathologic plugging of the dermal lymphatics with tumor emboli, or the extent of disease (EOD) codes EOD-E70 or EOD-E 710–730.

Population-Based Incidence Data

SEER*Stat version 8.3.4 software was used to calculate incidence rates with standard errors (SE) using age-adjusted to the 2000 US standard population, and then expressed per 100,000 person-years. Relative risks for tumor characteristics are expressed as incidence rate ratios (RRs), where a given characteristic is compared to a referent characteristic with an assigned RR of 1.0. Age-specific incidence rate curves were charted on a log-log scale. The age-adjusted rate is a weighted average of crude rates, where the crude rates are calculated for different age groups, and the weights are the proportions of persons in the corresponding age groups of a standard population as constructed by previous studies (Anderson et al., 2005).

Statistical Analysis

The covariates included in these analyses were limited to those available in the SEER program data. Demographic statistics included race, age at diagnosis, and year of diagnosis. Tumor characteristics included laterality, tumor size, lymph node status, AJCC stage, histological grade, ER status, and PR status.

Rate ratios (RRs) were calculated by dividing the age-adjusted breast cancer incidence rate among women with a high-risk prognostic factor by the incidence rate in women with the corresponding low-risk prognostic factor. Low-risk prognostic factors were assigned a rate ratio
of 1.0 and served as the reference group. Differences in the rate ratios for patient demographics and tumor characteristics were evaluated using 95% confidence limits that were calculated as previously described (Miettinen et al., 1985).

For analysis of overall survival, the time from diagnosis until the end of the follow-up was used together with the information whether a patient died or not. For cancer-specific survival, cancer-associated deaths were counted for the estimation of the cancer-specific survival whereas other deaths unrelated were censored. The censoring was based on the coding of these endpoints in the SEER database.

Seer*Stat was used to calculate 5-year relative survival using 60 monthly intervals for regional stage female inflammatory breast cancer diagnosed between 2008 and 2014 in the SEER 13 Registries. Results present annual observed, expected, and relative cumulative survival in both summary and detailed life tables. Age standardized statistics was included in this analysis. The International Cancer Survival Standard 1 - Ages 15+ for the Std Case Distribution and the default age variable (Age Standard for Survival (15-44,45-54,55-64,65-74,75+)) was used. This is the appropriate standard for breast cancer. Standard 1 was developed for cancer sites with increasing incidence by age. These life tables are the default for databases that do not include diagnosis years prior to 1992 (SEER 13) and are recommended when producing statistics limited to 1992+, or by or for limited geographies, or if producing statistics for race/ethnicity groups other than All, White, Black.
Chapter III

Results

Descriptive Statistics

A total of 300,174 Caucasian and 37,262 Hispanic women with inflammatory breast cancer were identified in this analysis, according to the inclusion and exclusion criteria stated in Chapter II Materials and Methods. This represents .13 % of total Caucasian women and .07 % of total Hispanic women diagnosed with cancer in the US between 1992 and 2014. All of the demographic and differences tumor characteristics are shown in Table 1. I found notable differences in the demographic characteristics between the Caucasian and Hispanic patients. The mean age of diagnosis for Caucasian women was 58.5 years and the mean age of diagnosis for Hispanic women was 54.6 years. 11% of Hispanic patients compared to 6% of Caucasian patients were diagnosed between 20 to 39 years old. 53% of Hispanic patients compared to 45% of Caucasian patients were diagnosed between 40 to 59 years old. Among Hispanic women, the RR for being diagnosed with IBC between 40 to 59 years old compared to 20 to 39 years old was $RR = 7.1$ (95% CI = 6.8 to 7.3) and RR for Caucasian women was $RR = 7.4$ (95% CI = 7.3 to 7.5).

49% Caucasian women were seen to have a later year of diagnosis between the ages of 60 to 79 years old compared to 36% of Hispanic women. Among Caucasian women, the RR for being diagnosed with IBC between 60 to 79 years old compared to 20 to 39 years old was $RR = 15.2$ (95% CI = 14.9 to 15.4) and RR for Hispanic women was $RR = 13.2$ (95% CI = 12.8 to
13.7). Between the first half (1992-2002) and the second half (2003-2014) of this study a 10% increase in diagnosis was seen Caucasian women whereas there was a 30% increase in Hispanic women between the first and second half of this study. Histological grade I and II were similarly distributed between the two races, however, more Hispanic women (42%) were diagnosed at histological grade III than Caucasian women (35%). The RR of Histological grade II compared to Histological grade I for Caucasian women is RR = 2.17 (95% CI =2.15 to 2.19) and for Hispanic women is RR = 2.49 (95% CI = 2.41 to 2.58).

The majority of both Caucasian women (62%) and Hispanic women (51%) were likely to present with smaller tumors (0-2 cm) at diagnosis. Among Caucasian patients the RR for being diagnosed with 2-5cm tumor compared to a 0-2cm tumor was RR = 0.39 (95% CI = 0.38 to 0.40) and among Hispanic patients the RR = 0.51 (95% CI = 0.46 to 0.57). The RR for being diagnosed with >5cm tumor compared to a 0-2cm tumor for Caucasian patients is RR = 0.05 (95% CI = 0.04 to 0.05) and RR = 0.16 (95% CI = 0.13 to 0.19) for Hispanic patients. Both Hispanic and Caucasian women were more likely to be diagnosed with estrogen receptor (ER) positive and progesterone receptor (PR) positive tumors. Caucasian women had a slightly higher percentage of (ER) positive (70%) (PR) positive (60%) tumors compared to Hispanic women who had (64%) (ER) positive and (55%) (PR) positive tumors. Among Caucasian patients the RR for being (ER) negative compared to (ER) positive was 0.28 (95% CI = 0.28 to 0.29) and among Hispanic patients the RR for being (ER) negative compared to (ER) positive was 0.34 (95% CI = 0.33 to 0.35). There was no significant difference in laterality in either Caucasian or Hispanic women.
Table 1. Number of cases of Inflammatory Breast Cancer (IBC) by patient demographics, tumor characteristics, and hormone receptor status.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Caucasian (n=300,174) n (%)</th>
<th>RR (95% CI)</th>
<th>Hispanic (n=37,262) n (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean) (years)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>58.5</td>
<td></td>
<td></td>
<td>54.6</td>
<td></td>
</tr>
<tr>
<td><strong>Age at Diagnosis (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-39</td>
<td>18,487 (6)</td>
<td>1.0 (Referent)</td>
<td>4,175 (11)</td>
<td>1.0 (Referent)</td>
</tr>
<tr>
<td>40-59</td>
<td>135,746 (45)</td>
<td>7.4(7.3-7.5)</td>
<td>19,681 (53)</td>
<td>7.1(6.8-7.3)</td>
</tr>
<tr>
<td>60-79</td>
<td>145,941 (49)</td>
<td>15.2(14.9-15.4)</td>
<td>13,406 (36)</td>
<td>13.2(12.8-13.7)</td>
</tr>
<tr>
<td><strong>Laterality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>146,626 (49)</td>
<td>1.0 (Referent)</td>
<td>18,122 (49)</td>
<td>1.0 (Referent)</td>
</tr>
<tr>
<td>Left</td>
<td>150,834 (50)</td>
<td>1.03 (1.02-1.04)</td>
<td>18,793 (51)</td>
<td>1.04(1.02-1.06)</td>
</tr>
<tr>
<td><strong>Tumor Size (cm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>184,616 (62)</td>
<td>1.0 (Referent)</td>
<td>18,846 (51)</td>
<td>1.0 (Referent)</td>
</tr>
<tr>
<td>2-5</td>
<td>79,693 (27)</td>
<td>0.39(0.38-0.40)</td>
<td>12,724 (34)</td>
<td>0.51(0.46-0.57)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>13,289 (4.2)</td>
<td>0.05(0.04-0.05)</td>
<td>2,208 (6.0)</td>
<td>0.16(0.13-0.19)</td>
</tr>
<tr>
<td>Unknown</td>
<td>21,812(7.2)</td>
<td>2.79(2.72-2.87)</td>
<td>2,965 (8.0)</td>
<td>3.35(3.10-3.62)</td>
</tr>
<tr>
<td><strong>Histologic Grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>54,847 (18)</td>
<td>1.0 (Referent)</td>
<td>5,245 (14)</td>
<td>1.0 (Referent)</td>
</tr>
<tr>
<td>II</td>
<td>118,015 (39)</td>
<td>2.17(2.15-2.19)</td>
<td>13,571 (36)</td>
<td>2.49(2.41-2.58)</td>
</tr>
<tr>
<td>III</td>
<td>104,746 (35)</td>
<td>1.94(1.92-1.96)</td>
<td>15,709 (42)</td>
<td>2.68(2.60-2.77)</td>
</tr>
<tr>
<td>IV</td>
<td>3,924 (1.3)</td>
<td>0.07(0.07-0.08)</td>
<td>496 (1.3)</td>
<td>0.08(0.07-0.09)</td>
</tr>
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</table>
**ER Status**

<table>
<thead>
<tr>
<th>Status</th>
<th>Rate (Rates)</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>210,137 (70)</td>
<td>1.0</td>
<td>(Referent)</td>
</tr>
<tr>
<td>Negative</td>
<td>59,163 (20)</td>
<td>0.28</td>
<td>(0.28-0.29)</td>
</tr>
</tbody>
</table>

**PR Status**

<table>
<thead>
<tr>
<th>Status</th>
<th>Rate (Rates)</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>180,467 (60)</td>
<td>1.0</td>
<td>(Referent)</td>
</tr>
<tr>
<td>Negative</td>
<td>84,255 (28)</td>
<td>0.47</td>
<td>(0.46-0.47)</td>
</tr>
</tbody>
</table>

RR = rate ratio; CI = confidence interval; AJCC = American Joint Committee on Cancer; ER = estrogen receptor; PR = progesterone receptor. Rates refer to age-adjusted incidence rates and are expressed per 100 000 woman-years.

Comparison of Survival Between Caucasian and Hispanic Patients

Figure 1 displays an age-specific incidence rate curve. For both Caucasian and Hispanic women inflammatory breast cancers cases rise rapidly until age 65 years then remained constant. Substantial differences in the age-specific rates between the two races were evident among patients older than 45 years of age. Age at diagnosis was similarly distributed between the two races until 35 years of age where an increase in rate was seen in Caucasian women compared to Hispanic women.
Figure 1
Age-specific incidence rates of inflammatory breast cancer per 100,000 woman-years among Hispanic and Caucasian women 20 to 79 years old

Figure 2 displays cases diagnosed during the years 1992 to 2014 and shows a rising (though non-significant) trend for IBC. Hispanic women displayed a lower incidence rate compared to Caucasian women. Caucasian women saw gradual increase from 1993 to 1998, which was the highest incidence rate, then a decrease from 1999 to 2003, which was the lowest incidence rate. Whereas Hispanic women demonstrated less notable change. Years 2005 to 2014 displayed a slight increase with a noticeable decrease in 2011 for both races.
Figure 2
Trends for age-adjusted incidence rates for inflammatory breast cancer (IBC) cases among Hispanic and Caucasian women, diagnosed during the years 1992 to 2014

Figure 3 shows cause specific survival for IBC from 1 to 5 years after diagnosis. The Caucasian and Hispanic women showed no significant differences between percent survival. Both races displayed a similar continuous decrease in percent survival during the 5-years post diagnosis. After 1 year both displayed 85% survival and after 5 years, that percentage was reduced to 40% survival with Hispanic women having a slightly lower survival rate.
Figure 4 shows trends in the age-standardized incidence rates by ER and PR status. 9.5% of Caucasian women and 11.3% of Hispanic women with missing data on ER hormone receptors and who were borderline were excluded in this study and 12% of Caucasian women and 13.8% of Hispanic women with missing data on PR hormone receptors and who were borderline were excluded in this study. Hispanic women had lower incidence rate of ER+ tumors compared to Caucasian women (Fig 4a). From 1992 to 2014 ER+ incidence increased for both races at a similar rate. Between 1995 to 2003 Caucasian women saw a significant increase
in ER+ tumors that then drop in 2003 before increasing again in 2004 and continued to climb at a steady rate. While Caucasian women saw an increase between 1995 and 2003, Hispanic ER+ incidence plateaued and then increased between 2004 to 2014, similarly to Caucasian women.

Similar to the incidence rates for ER+ tumors, those for PR+ tumors increased significantly per year from 1992 to 2014 for both races (Fig 4c). Caucasian women had higher incidence rate of PR+ tumors compared to Hispanic women. The incidence rate for ER- tumors is lower for both races compared to the ER+ tumors (Fig 4b). Hispanic women had a lower incidence rate of ER- tumors compared to Caucasian women. Between 2003 and 2005 there was a sharp increase and then decrease in ER- between 2005 and 2010 for both races. PR- incidence rates were similar to ER- incidence rates (Fig 4d). Caucasian women had a higher incidence than Hispanic women. There was an increase in PR- tumors in 2003 and then a decrease in 2006 for both races.
Figure 4
Trends in the age-standardized incidence rates by ER and PR status among Hispanic and Caucasian women, 1992-2014

a) Trend by ER+ status; b) Trend by ER- status; c) Trend by PR+ status; d) Trend by PR- status
Estrogen Receptor Status

Rate per 100,000 Women

Year of Diagnosis

Caucasian ER-  Hispanic ER-
d.

Progestin Receptor Status

Rate per 100,000 Women

Year of Diagnosis

Caucasian PR-  Hispanic PR-
Chapter IV
Discussion

Significance of Results

The SEER database is an essential population-based resource for understanding the implications of cancer diagnoses between demographic groups, geographic regions, and time. SEER presents novel insights into the study and practice of oncology in the U.S that are not attainable through other sources. The program is developing methods to investigate further biomarker data, results from special populations, and expand bio-specimen banking to allow innovative cancer research that can advance oncology study (Bohn et al., 2018).

This study revealed slight differences in the presentation of inflammatory breast cancer between Caucasian women and Hispanic women in the U.S. My finding of a younger age at onset of IBC among Hispanic women as compared to Caucasian women is consistent with previous studies involving the comparison of Hispanic women to other racial groups (Wingo et al. 2004; Hirko et al., 2013). More than half of the IBC cases among Hispanic occurred before the age of 60, whereas almost half of the IBC cases among Caucasian happened after the age of 60. These findings highlight the limitation of using the proportion of IBC out of all breast cancer instead of IBC incidence rates to assess racial differences. Risk factors can partly explain the racial disparities in IBC between Caucasian women and Hispanic women described in this study. For example, several reproductive factors have been discovered to be associated with IBC diagnosis in prior studies. Studies have shown IBC patients to have a younger age at menarche.
and a younger age at first birth as compared to non-inflammatory breast cancer and non-breast cancer patients (Mourali et al. 1980; Chang et al. 1998a; Boussen et al. 2010b; Chang et al. 1998b; Le et al. 2006; Levine 2004; Hirko, 2013). Additionally, another study showed that the duration of breastfeeding surpassing 24 months was found to be significantly associated with IBC (Le et al. 2005). If these reproductive agents are risk factors for IBC and vary by race, it could explain some of the disparities in IBC between Caucasian and Hispanic women observed in this study.

In addition to reproductive risk factors for IBC, another study revealed obesity to be a risk factor for premenopausal IBC but not for premenopausal non-IBC (Levine & Veneroso 2005), while another study demonstrated that IBC patients had significantly higher BMI than both non-IBC patients and non-breast cancer patients unbiased to menopausal state (Chang et al. 1998b). Therefore, it is possible that some of the difference in the proportion of IBC by race may be explained by differences in risk factors that are not accounted for in this study.

I found that the relative cancer-specific survival for inflammatory breast cancer of Hispanic women was similar to that of Caucasian women. The findings in this study showed that Hispanic women, although younger, had a similar age at diagnosis as Caucasian women (Table 1). The similarity in age at diagnosis can account for the similarities in the relative cancer-specific survival rates between the two races evaluated in this study (Figure 3).

Although the incidence of IBC is significantly lower in Hispanic women compared to that of Caucasian women, this may increase if Hispanic women develop similar lifestyle
behaviors to that of Caucasian women. There are several lifestyle and non-lifestyle factors which influence the likelihood of developing IBC, such as weight management, age at first birth, number of offsprings, breastfeeding duration, menstrual history, reproductive factors, as well as genetics, family history, and diet and exercise (Power et al., 2018). Hispanic women display differences in several of these risk factors compared to Caucasian women (Hines, 2010), which may explain their current lower levels of inflammatory breast cancer incidence.

However, Hispanic women also face disparities in screening and genetic testing related to breast cancer compared to Caucasian women (Davis et al., 2017). The Hispanic community is more susceptible to facing challenges related to healthcare access, insurance coverage, and a higher prevalence of unmet healthcare needs (Okoro et al., 2017). This may account for lower incidence rates among Hispanic women compared to Caucasian women due to inadequate access to breast cancer screening and thus diagnosis.

Research Limitations

The potential limitations of this study include missing or incomplete data on specific cancer risk and treatment and inaccuracies and incompleteness of the data collected from the registries. There are a number of issues that influence the collection and interpretation of cancer registry data. For instance, cancer registries record cancer cases, not patients and this can lead to error when a patient has multiple cancer diagnoses who appear more than once in a registry.
database. Another error that can be found when interpreting cancer registry data is duplicate reports, where the same cancer is diagnosed and recorded by more than one physician.

Another limitation is the use of different laboratories that use different methods to determine hormonal receptor status can result in non-standardized measurement of hormone receptor expression. Because there are no standard laboratories or histopathologic slide review for diagnostic confirmation these databases could be influenced by differential misclassification or detection rates, incomplete or non-standardized data. The lack of data for menstrual status, reproductive risk factors, obesity, methods of detection, and treatment are also limitations to this study. Without information about the method of exposure, it is not possible to distinguish between the impact of increased clinical awareness and screening mammography on the trends in IBC incidence. The SEER database does not show information about reproductive risk factors; however, it does provide information on the most critical risk factor for female breast cancer, which is age at diagnosis.

Another limitation is the misassignment of race/ethnicity because difficulties can arise in coding race/ethnicity in a registry database. This is due to race recognition, methodologies, and the fact that populations change over time. Because a consistent method of evaluating and coding race/ethnicity does not exist this can lead to faulty results.
Conclusion

With the lack of epidemiologic data on IBC, this analysis represents progress to the understanding of this rare and aggressive disease. By evaluating racial disparities in IBC occurrence between Caucasian women and Hispanic women, I aim to produce additional predictions about potentially modifiable risk factors for IBC. The presence of many modifiable risk factors makes IBC a model disease for preventive interventions. Resources are more effectively utilized in prevention approaches than in treating advanced IBC. The risk of breast cancer can be lessened by adjustments in diet, exercise, weight management, and preventive health screening. More programs dedicated to the health of Hispanic women should be employed to increase education and implement risk reduction strategies and preventative screening among Hispanic women. Hispanics are one the largest groups in the US and keeping incidence low and reducing cancer-related mortality could have a substantial impact nationwide. These conclusions reveal the need for further studies to reach a better understanding of factors that impact IBC development among Hispanics, as well as other ethnic and racial groups. Future research should focus on etiologic factors that may underlie these differences and also examine country of origin and date of immigration to the U.S. to further understand potentially modifiable risk factors for IBC.
Appendix

Definition Of Terms:

Anaplastic: cancer cells that divide rapidly and have little or no resemblance to normal cells.

Axillary: Pertaining to the armpit, the cavity beneath the junction of the arm and the body.

Bilateral: Breast cancer that involves both breasts.

Cancer Prevalence: The number of living people who have ever been diagnosed with cancer. It also includes people diagnosed with cancer in the past as well those who were recently diagnosed.

Carcinoma: A malignant tumour of the epithelium, the tissue that lines the skin and internal organs of the body.

Clinical Staging: Stage 1 of the AJCC staging- Determines how much cancer there is based on the physical examination, imaging tests, and biopsies of affected areas.

Covariate: a variable that is observed rather than manipulated but can affect the outcome of an experiment or study

Dermal lymphatic invasion (DLI): Ecstatic dermal lymphatic vessel with tumor cell aggregates. Dermal lymphatic invasion is the most characteristic pathologic feature of IBC.

Disseminated Tumor Cells (DTCs): The finding of single tumor cells or small tumor cell groups in the lymph, blood (including bone marrow aspirations) and secondary organs.

Emboli: Something that travels through the bloodstream, lodges in a blood vessel and blocks it.

Histologic Grade: A description of a tumor based on how abnormal the cancer cells and tissue look under a microscope and how quickly the cancer cells are likely to grow and spread. A Histologic grade is assigned to a patient’s cancerous breast tumor to identify the type of tumor present and help determine the patient’s prognosis (projected outcome).

Estrogen-Receptor (ER): a group of proteins found inside cells. They are receptors that are activated by estrogens (17β-estradiol). If a breast cancer is estrogen-receptor positive it means that estrogen may be supporting the growth and spread of the cancer cells.

Inflammatory Breast Cancer (IBC): Inflammatory breast cancer is a rare and very aggressive disease in which cancer cells block lymph vessels in the skin of the breast. This type of breast cancer is called “inflammatory” because the breast often looks swollen and red, or inflamed.
In situ: malignant cells are present as a tumor but have not metastasized, or invaded, beyond the basement membrane of where the tumor was discovered.

Invasive Ductal Carcinoma (IDC): Also known as infiltrating ductal carcinoma, is cancer that began growing in a milk duct and has invaded the fibrous or fatty tissue of the breast outside of the duct. IDC is the most common form of breast cancer, representing 80 percent of all breast cancer diagnoses.

Laterality: describes the side of a paired organ or side of the body on which the reportable tumor originated.

Lymph Node Status: shows whether or not the lymph nodes in the underarm area (axillary nodes) contain cancer:

- Lymph node-negative means the lymph nodes do not contain cancer.
- Lymph node-positive means the lymph nodes contain cancer.

Malignant Tumor: A tumor that invades surrounding tissues, is usually capable of producing metastases, may recur after attempted removal, and is likely to cause death unless adequately treated.

Metastatic: The spread of a disease-producing agency (such as cancer cells) from the initial or primary site of disease to another part of the body.

Pathologic: Altered or caused by disease.

Pathologic Staging: Stage 2 of the AJCC staging- can only be determined from individual patients who have had surgery to remove a tumor or explore the extent of the cancer. Pathologic staging combines the results of both the clinical staging (physical exam, imaging test) with surgical results.

Post-Therapy or Post-Neoadjuvant Therapy Staging: Stage 3 of the AJCC staging- determines how much cancer remains after a patient is first treated with systemic (chemotherapy or hormone therapy) and/or radiation therapy prior to their surgery or where no surgery is performed. This can be assessed by clinical staging guidelines and/or pathologic staging guidelines.
Progesterone-Receptor (PR): is a protein found inside cells. It is activated by the steroid hormone progesterone. If breast cancers are PR positive it means that progesterone may be supporting the growth and spread of the cancer cells.

Restaging: Stage 4 of the AJCC staging- is used to determine the extent of the disease if a cancer comes back after treatment. Restaging helps determine the best treatment options for cancer that has returned.

Undifferentiated Cancer: A cancer in which the cells are very immature and "primitive" and do not look like cells in the tissue from it arose. As a rule, an undifferentiated cancer is more malignant than a cancer of that type which is well differentiated. Undifferentiated cells are said to be anaplastic.

Unilateral Breast Cancer: Breast cancer that involve one breast
References


