2014

Risk factors for developing inflammatory breast cancer: an epidemiological study of a single patient population

White, Randie Elizabeth

http://hdl.handle.net/2144/14382

Boston University
BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

RISK FACTORS FOR DEVELOPING INFLAMMATORY BREAST CANCER:
AN EPIDEMIOLOGIC STUDY OF A SINGLE PATIENT POPULATION

by

RANDIE E. WHITE

B.S., Boston College, 2012

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science
2014
First Reader
David Seldin, M.D. Ph.D
Chief, Section of Hematology-Oncology
Boston Medical Center

Second Reader
Beth Overmoyer, M.D., FACP
Director, Inflammatory Breast Cancer Program
Susan F. Smith Center for Women’s Cancers at Dana Farber
Assistant Professor of Medicine
Harvard Medical School
DEDICATION

I would like to dedicate this work to my parents. Thank you for your constant support and encouragement.
ACKNOWLEDGMENTS

I would like to sincerely thank Dr. Beth Overmoyer for all of her guidance, instruction, encouragement, and excitement in this project. I would also like to thank Dr. Jennifer Bellon, Dr. Laura Warren, Dr. Diana Caragancianu, Dr. Eren Yeh, Dr. Faina Nakhlis, Dr. Heather Jacene and everyone in the Inflammatory Breast Cancer Unit at Dana Farber Cancer Institute in Boston, MA who were involved in creating and implementing this IBC database and allowing me to be a part of their research.
RISK FACTORS FOR DEVELOPING INFLAMMATORY BREAST CANCER: AN EPIDEMIOLOGIC STUDY OF A SINGLE PATIENT POPULATION

RANDIE E. WHITE

ABSTRACT

Inflammatory breast cancer (IBC) is a rare and aggressive form of breast cancer, with a particularly poor prognosis. Identification of epidemiologic risk factors for IBC might shed light on causes of the disease, and guide screening and perhaps treatment. Previous studies have suggested that race, geographic location, body mass index (BMI), menopausal status, age at menarche, parity, duration of lactation, and exposure to mouse mammary tumor virus may be key risk factors in the development of IBC. This retrospective epidemiologic study examines the risk factors for IBC in predominantly Caucasian patients treated at the Dana Farber Cancer Institute (DFCI) in Boston, MA. The risk factors that were examined in this study include the following: BMI, family history of having breast cancer, comorbidities, duration of symptoms associated with IBC prior to diagnosis, season of diagnosis, and molecular subtypes of breast cancer. Additionally, the descriptive statistics for the mean age of diagnosis, race, menopausal status, genetic predisposition, and the presence of metastases in distant organs were also determined. This study showed that there is some evidence of a hereditary component and seasonal variation to the disease. Furthermore, this study reiterates the association of high body mass index (BMI) and IBC. The data collected from the DFCI IBC patient population suggest that modifiable lifestyle factors, perhaps due to a lack of awareness of the disease, might be crucial in the development of IBC. Further research is needed to
explore the unique risk factors in developing IBC elucidated in this study in order to better understand and prevent such an aggressive disease.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>TITLE</th>
<th>viii</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPYRIGHT PAGE</td>
<td>ii</td>
</tr>
<tr>
<td>READER APPROVAL PAGE</td>
<td>iii</td>
</tr>
<tr>
<td>DEDICATION</td>
<td>iv</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>v</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>vi</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>viii</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>x</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>xi</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>xii</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>Risk Factors of Inflammatory Breast Cancer</td>
<td>5</td>
</tr>
<tr>
<td>Race</td>
<td>5</td>
</tr>
<tr>
<td>Residency, Geographic Location and Socioeconomic Status</td>
<td>13</td>
</tr>
<tr>
<td>Obesity</td>
<td>17</td>
</tr>
<tr>
<td>Menopausal Status</td>
<td>22</td>
</tr>
<tr>
<td>Age of Menarche, Pregnancy and Lactation</td>
<td>23</td>
</tr>
<tr>
<td>First Degree Family History and High Mammographic Breast Density</td>
<td>25</td>
</tr>
<tr>
<td>Additional Risk Factors</td>
<td>26</td>
</tr>
</tbody>
</table>
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rates of IBC and non-inflammatory LABC by race</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>Genetic predispositions and family history</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>Trends of association of BMI, smoking status, and comorbidities at time of diagnosis</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>Menopausal status and BMI</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>Population of patients with diabetes</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>Receptor composition of metastatic patients</td>
<td>58</td>
</tr>
<tr>
<td>Figure</td>
<td>Description</td>
<td>Page</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td>1</td>
<td>Age-specific incidence rates of non-IBC breast cancer versus IBC per 100,000 woman-years</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Survival rates of IBC patients by race</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>Survival curves of postmenopausal IBC patients by obesity status</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>Race and menopausal status</td>
<td>34</td>
</tr>
<tr>
<td>5</td>
<td>Family history</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>Genetic predispositions</td>
<td>38</td>
</tr>
<tr>
<td>7</td>
<td>BMI</td>
<td>41</td>
</tr>
<tr>
<td>8</td>
<td>Comorbidities</td>
<td>46</td>
</tr>
<tr>
<td>9</td>
<td>Duration of symptoms for IBC patients</td>
<td>49</td>
</tr>
<tr>
<td>10</td>
<td>Season of diagnosis</td>
<td>51</td>
</tr>
<tr>
<td>11</td>
<td>Breast cancer subtypes</td>
<td>53</td>
</tr>
<tr>
<td>12</td>
<td>Metastatic status at time of presentation and location of metastases</td>
<td>55, 56</td>
</tr>
</tbody>
</table>
### LIST OF ABBREVIATIONS

- **BMI**: Body Mass Index
- **BWH**: Brigham and Women’s Hospital
- **CNS**: Central Nervous System
- **DFCI**: Dana Farber Cancer Institute
- **DFS**: Disease Free Survival
- **ER**: Estrogen Receptor
- **GDP**: Gross Domestic Product
- **HER2**: Human Epidermal Growth Factor Receptor 2
- **IBC**: Inflammatory Breast Cancer
- **IGF-I**: Insulin-like Growth Factor-I
- **IRB**: Institutional Review Board
- **LABC**: Locally Advanced Breast Cancer
- **MMTV**: Mouse Mammary Tumor Virus
- **NCI**: National Cancer Institute
- **OS**: Overall Survival
- **PEV**: Pousée Evolutive
- **PI**: Principle Investigator
- **PR**: Progesterone Receptor
- **SEER**: Screening, Epidemiology, and End Results Program
- **SES**: Socioeconomic Status
- **TN**: Triple Negative (ER-/PR-/HER2-)
INTRODUCTION

Inflammatory breast cancer (IBC) is a rare form of breast cancer; it is a clinical diagnosis made in the setting of confirmed breast cancer, characterized by rapid changes of the breast including a display of inflammatory signs involving more than one third of the breast: skin erythema, edema, warmth, and peau d’orange (thickening of the skin of the breast characterized as being similar to an orange peel). Additionally, a tumor mass is frequently absent (Overmoyer et al., in press). IBC is aggressive and rapidly progressive – patients present with stage IIIB/C, i.e. locally advanced, or stage IV breast cancer. 20-40% of patients have metastatic disease on presentation (stage IV) and the initial symptoms involving the breast are usually not present for longer than six months. Frequently, patients present after having a duration of symptoms of less than three months. Tumor emboli found in the dermal lymphatics are the cause of changes in the breast, only detected or confirmed in 75% of patients. The presence of tumor emboli occluding the dermal lymphatics results in edema and erythema of the skin and enlargement of the breast as a whole (Anderson et al., 2005-2006; Wingo et al., 2004).

Biologically, IBC typically displays highly proliferative molecular subtypes, such as HER2-overexpressing subtypes or triple negative breast cancer: defined as estrogen receptor (ER)- negative, progesterone receptor (PR)- negative, and human epidermal growth factor receptor 2 (HER2)- negative (Overmoyer et al., in press). Hormone receptors are important in understanding the nature of the breast cancer and therefore treatment options. Breast cancer that is positive for estrogen or progesterone receptors generates intracellular signals governed by hormonal mechanisms that promote their
growth. Blocking these hormones can therefore help to abate the cancer (breastcancer.org, 2013). In contrast, breast cancer that is triple negative functions through an unknown signaling pathway, making it more difficult to treat. HER2- positive breast cancer, another highly proliferative subtype, overexpresses the human epidermal growth factor receptor type 2, which promotes growth of cancer cells. Similarly to triple negative breast cancer, HER2 overexpressing breast cancer is less responsive to hormone therapy, but can be successfully treated with HER2-directed therapy (mayoclinic.org, 2012).

Additionally, IBC is associated with a number of biologically unique features, such as: a high frequency of mutations of the tumor suppression gene, p53, which regulates the cell cycle; overexpression of the cell adhesion protein E-cadherin, overexpression of a protein involved in cytoskeleton rearrangement, RhoC GTPase; loss of expression of Wisp3, a gene that is part of a family of tumor suppressor genes, which act as negative regulators of cell division and abnormal growth; and extensive angiogenesis (growth of blood vessels) (Dawood et al., 2011; Overmoyer et al., in press). It is evident that these molecular abnormalities are important in developing the highly aggressive and frequently metastatic profile associated with IBC.

IBC accounts for 2-5% of all breast cancers in the United States; the incidence increases in women until 50 years of age and then plateaus (Figure 1). Figure 1 is taken from a study performed by Hance et al., which looked at changes in incidence rates over 3 year intervals by breast cancer subtype using the Surveillance, Epidemiology, and End Results Program (SEER) database between 1988-2000. This National Cancer Institute
(NCI) sponsored program provides information on cancer statistics in the U.S. population. Researches noted differences in age-specific incidence rates in patients older than 50, with rates in IBC patients reaching a plateau, whereas rates in non-IBC locally advanced breast cancer (LABC) patients continued to rise. It has been shown that the incidence of non-IBC breast cancer continues to increase, although at a slower rate, after 50 years of age (Figure 1) (Overmoyer et al., in press). Whereas IBC accounts for 2% of newly diagnosed cancers, it accounts for 7% of all breast-cancer specific mortality in the U.S. with a 5-year survival of less than 40%, thus proportionally more deaths are related to IBC than to non-IBC (Lo et al., 2007). The incidence of IBC varies between populations, ethnicities, and geographic locations (Hance et al., 2005). Patients with IBC can present at any age and are usually younger than non-IBC breast cancer patients, usually presenting between the ages of 45 and 57, with a mean age of 57 years. This is significantly younger than the mean age of 62 seen in non-IBC breast cancer (Anderson et al., 2005-2006; Overmoyer et al., in press). Similar to the incidence of IBC, the mean age at diagnosis varies between different patient populations (Anderson et al., 2005-2006).
Figure 1: Age-specific incidence rates of non-IBC breast cancer versus IBC per 100,000 woman-years. Using SEER data coding from SEER 9 Registries, 1988-2000, age specific incidence is plotted: A) by three malignant breast cancer types; B) by IBC definition (Figure taken from Hance et al., 2005).
Currently, IBC is a poorly understood subtype of breast cancer. According to the literature, possible risk factors include, to varying degrees, all of the following: race, geographic location, socioeconomic status (SES), obesity, menopausal status, age of menarche, age at first pregnancy, duration of lactation, family history, mammographic density, mouse mammary tumor virus (MMTV) exposure, environmental factors, and genetic factors. It is useful to study IBC patient populations to help determine the potential risk factors associated with IBC, because it is such an aggressive disease, distinct from non-IBC breast cancer. Overall survival (OS) rates are less than 50%. Locoregional recurrence is also more common in IBC compared to non-IBC (Overmoyer et al., in press). Comparing IBC to non-IBC, 89.2% of non-IBC patients survive for 5 years after diagnosis according to a SEER statistics fact sheet, while only 34% of IBC patients survive 5 years (NIH, 2014). It is a disease with diverse epidemiologic characteristics that differ among patient populations. So much is unknown about IBC, yet studying the epidemiology of this disease is extremely important to identify risk factors and to gain a better understanding of its biology. This could help to guide screening and treatment decisions. Furthermore, because IBC has an unknown etiology, it is possible that modifiable lifestyle characteristics may be key factors in lessening the risk of this disease. The following introduction will examine the risk factors associated with IBC found in the literature.

RISK FACTORS OF INFLAMMATORY BREAST CANCER

Race
Using SEER 9 registries from 1988-2000, Hance et al. looked at the trends among IBC patients of different races. They found that IBC incidence rates were higher among African American women than Caucasian women, 2.5 and 2.0 per 100,000 women, respectively (Hance et al., 2005). This data appears consistently throughout the literature. It is important to note, however, that a racial disparity also exists in non-IBC breast cancer. The number of new cases of all types of female breast cancer per year per 100,000 women between 2000-2004 was 132.5 and 127.8 for African Americans and Caucasians, respectively (CDC, 2008). Research performed across equal-access healthcare systems supports the hypothesis that the African American race itself can be an independent predictor for an increased risk of developing IBC (Hance et al., 2005). One potential cause of racial disparity is economic. Comparing Hispanics to African Americans, Hispanics have similar rates of poverty in the U.S. as African Americans: three-fold greater than Caucasians. Their incidence of IBC, however, is similar to that of Caucasian women, which is another indication that race is likely to be an independent predictor of IBC risk (Il’yasova et al., 2011). Data depicting the African American race as a risk factor for IBC has been analyzed across multiple institutions to determine racial disparities and possible causes of these racial disparities (Table 1).
Table 1: Rates of IBC and non-inflamatory LABC by race. Incidence rates by race, expressed as number of incidence cases per 100,000 women per year, adjusted for age (Table taken from Il’yasova et al., 2011).

<table>
<thead>
<tr>
<th></th>
<th>IBC</th>
<th>Non-inflamatory LABC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Rate (95% CI)</td>
<td>Number</td>
</tr>
<tr>
<td>All</td>
<td>2,942</td>
<td>2.59 (2.50-2.69)</td>
<td>5755</td>
</tr>
<tr>
<td>African Americans</td>
<td>453</td>
<td>3.91 (3.56-4.30)</td>
<td>934</td>
</tr>
<tr>
<td>Non-Hispanic Whites</td>
<td>1,920</td>
<td>2.54 (2.42-2.65)</td>
<td>3729</td>
</tr>
<tr>
<td>Hispanic Whites</td>
<td>475</td>
<td>2.51 (2.26-2.80)</td>
<td>580</td>
</tr>
<tr>
<td>Other</td>
<td>194</td>
<td>1.59 (1.37-1.83)</td>
<td>512</td>
</tr>
</tbody>
</table>
Age of diagnosis also demonstrates the racial disparity that exists among IBC patients. Looking at SEER registries, the median age of IBC diagnosis is 58 years for Caucasians, 54 years for African Americans and Asian Pacific Islanders, and 49.5 years for American Indians and Alaskan Natives (Anderson et al., 2005). Hirko et al. used SEER data from 1988-2008 and determined that although Hispanics have a similar incidence of IBC compared to non-Hispanic whites, they have a younger mean age of diagnosis. The mean age of diagnosis is 52.6 years for Hispanic women, 58.5 years for Arab Americans and 60.1 years for non-Hispanic whites (Hirko et al, 2013). The mean age of diagnosis among racial categories is an important discrepancy meriting further study because of modifiable lifestyle factors that may differ among ethnic groups. Additionally, there could be genetic differences among ethnic groups that account for these differences.

Subtypes of breast cancer are defined by their hormone receptors and human epidermal growth factor receptor 2 (HER2) statuses. In general, Luminal A breast cancer is HER2-negative, ER- positive and/or PR- positive. Luminal B breast cancer is HER2-positive, ER- positive and usually PR negative. Triple negative disease is HER2-negative, ER-negative, and PR- negative. HER2- overexpressing breast cancer is HER2-positive, ER-negative and PR- negative (Yang et al., 2007). IBC patients tend to have triple negative or HER2-overexpressing disease, which are the more proliferative subtypes of breast cancer (Overmoyer et al, in press). When comparing IBC to non-IBC locally advanced breast cancer (LABC), 24% of IBC were HER2-overexpressing and
22% were triple negative, while 14% of non-IBC LABC samples were HER2-overexpressing and 19% were triple negative (Overmoyer et al., in press).

Compared to Caucasians, all other racial groups are more likely to have triple negative IBC. IBC patients with ER-negative disease have a worse overall survival compared to ER-positive cancer, 2.0 years versus 4.0 years respectively (Hance et al., 2005; Hirko et al., 2013). African Americans patients who present with ER-negative IBC are significantly younger than Caucasian patients who present with ER-negative disease (Hance et al., 2005). Additionally, premenopausal African American women are at an even greater risk for developing triple negative IBC compared with postmenopausal African American patients, 39% versus 14%, respectively (Andic et al., 2011).

Overall, African American women present with more aggressive IBC than Caucasian women. Furthermore, African American women have a poorer IBC overall survival compared with Caucasian women: 3.0 versus 2.0 years, respectively. African American and Caucasian women have been shown to have equal responses to local and systemic therapy, but African American women with IBC have a higher rate of locoregional recurrence; further suggesting a biological determinant associated with race (Hance et al., 2005). When compared to Caucasian women, African American women with non-IBC breast cancer present with cancers having of higher histological grade cancers, which is an indication of tumor aggressiveness (Henson et al., 2003). Finally, African American women have a greater nodal involvement at diagnosis of IBC compared to Caucasian women (Andic et al, 2011). High-grade tumors are seen across all stages of breast cancer in African Americans. All of these findings have led to
speculation that low SES or access to healthcare is not the only cause of the racial disparity (Henson et al., 2003).

An examination of the data for Hispanic women with IBC shows that they present with larger tumors, tumors of a higher grade, and more positive lymph nodes than non-Hispanic Caucasians, according to Yang et al., 2009. It should be noted that while a higher percentage of Hispanics compared to Caucasians resided in an area where greater than 10% of the residents were under the federal poverty level, no difference in treatment modality existed (Yang et al., 2009). This is an important finding, suggesting the differences in cancer characteristics between Hispanic and non-Hispanic IBC patients were not due to different treatment regimens as a result of lack of access to healthcare.

Mean survival time differs among racial groups as well. After adjusting for age, hormone receptor status, HER2 status, and education level, Arab American women with IBC had the longest mean survival of 50.5 months while American Indians with IBC had the shortest mean survival of 24.8 months (Hirko et al., 2013). Non-IBC breast cancer mortality rates have been shown to be greater for African American compared with Caucasian women. These data are also consistent with breast cancer mortality rates among African American patients with IBC (Figure 2). Additionally, the 5-year relative risk of death among African American patients with non-IBC breast cancer treated in the U.S. Department of Defense healthcare system was 25%, versus 34% for African American patients diagnosed with breast cancer in the SEER registries. The SEER registries provide information on cancer statistics for the U.S. population. In contrast, those patients who received treatment from the U.S. Department of Defense healthcare
system are a smaller population of patients receiving treatment from one healthcare system. Much of the U.S. population does not have equal access to healthcare unlike those patients covered by the U.S. Department of Defense. This indicates that a lack of equal access to healthcare does have some influence on racial differences in mortality rate, but does not fully account for the racial disparities in survival statistics (Hance et al., 2005). Even after adjusting for stage and age, biological aggressiveness of the cancer seen in the African American race seems to have a substantial affect on outcome (Figure 2) (Andic et al., 2011).
Figure 2: Survival rates of IBC patients by race. Survival rates are plotted for African American women and Caucasian women who received the same treatment regimen for IBC (Figure taken from Yang et al., 2009).
Comorbidities, such as diabetes and hypertension, seem to be higher in some racial groups compared with others. In one population of non-metastatic IBC patients treated from 1995-2009 at Emory University, for example, 67% of African Americans versus 33% of Caucasians had significant comorbidities at the time of diagnosis. 26.7% of African Americans and only 12% of Caucasians had diabetes and 50% of African Americans, but only 16% of Caucasians had hypertension (Andic et al., 2011). In a second study population from the Florida Cancer Data Systems dataset, African Americans with IBC had twice the rate of diabetes compared to Caucasian women with IBC (Yang et al., 2009). The difference in comorbidities among racial groups could be an important factor in trying to explain the racial disparities that exist in the incidence of IBC, the age at time of diagnosis of IBC, and the molecular subtypes of IBC, leading to a better understanding of the disease itself. The higher rate of certain comorbidities, for example, could be the result of other modifiable lifestyle factors such as nutrition, diet and exercise. Some ethnic groups may be at an increased risk for IBC, not only because of a biological determinant, but also because of other health issues and therefore the risk factors may be compounded.

Residency, Geographic Location and Socioeconomic Status

Inflammatory breast cancer is more prevalent in certain parts of the world than in others. It also varies in rural versus urban settings. For example, IBC is more common in North African than in any other part of the world. Tunisia is a North African country of 11 million inhabitants, where 11,000 cases of cancer are diagnosed yearly. Breast cancer
is the most common malignancy in Tunisian women, with 1,500 cases diagnosed yearly. The incidence of IBC in Tunisia is 27-30 per 100,000 women, which is much greater than the incidence in the United States. IBC represents 5-7% of all breast cancers in Tunisia. Furthermore, the mean age of diagnosis of non-IBC breast cancer in Tunisia is 50 years of age with 11% of patients presenting younger than 35 years (Boussen et al. 2010). The mean age of diagnosis of IBC in Tunisia is 43 years with 22% of patients presenting younger than 35 years of age; a much younger age than that seen in the United States (Boussen et al. 2010).

Access to healthcare may affect incidence by affecting contributing factors to the development of the disease, such as obesity, comorbidities, or treatment outcome. There is a high predominance of rural life in Tunisia, affecting access to healthcare, which is vital to treating such an aggressive disease. Chaher et al. performed a study comparing Tunisian IBC patients to Algerian IBC patients. They discovered that while Algerian women living in rural versus urban environments had no difference in their frequencies of developing IBC, this was not the case in Tunisia. IBC in Tunisia was strongly associated with living in a rural region. Researchers speculated that socioeconomic factors, such private healthcare not being available to everyone in Tunisia, could be a factor. This is due to the fact that the rural population in Tunisia is economically poorer than the urban population. In contrast, Algeria has a healthcare system that covers the entire population, both urban and rural (Chaher et al., 2012). IBC incidence rates may also be affected by factors related to SES. In the last few decades, incidence of IBC in Tunisia has decreased, paralleling an increase in gross domestic product (GDP)
(Il’yasova et al., 2011). Living in any high poverty county, with a high percentage of the population not completing high school education, has been shown to be associated with IBC in the U.S.; even after adjusting for age and race. This could further support the premise that women with low SES have less access to healthcare and therefore may not have access to treatment soon after symptoms arise (Schlichting et al., 2012).

Researchers examined molecular characteristics of IBC in patients from Tunisia. 83% of Tunisian IBC lack hormone receptor expression (Dawood et al., 2012). There is a higher expression of EGF and HER2 overexpression in IBC. They are more likely to have p53 mutations and nuclear overexpression associated with a decreased response to chemotherapy, compared with other breast cancers matched for grade and stage (Houchens et al., 2008).

Egypt is another North African country with a high incidence of IBC. 11% of all breast cancers in Egypt are IBC (Hirko et al., 2013). Additionally, Egyptian IBC patients display a more aggressive form of the disease compared with patients in other countries that have been studied. Patients in Egypt, similarly to patients in Tunisia, have younger mean age of diagnosis of 46.9 years compared to the U.S. (Lo et al., 2008). According to Lo et al., there is a possible molecular or genetic difference between IBC in Egypt versus the U.S. IBC evaluated among Egyptian patients had a higher number of tumor emboli, a high level of the oncogene RhoC GTPase, and a larger percentage of patients present with a palpable tumor mass. Furthermore, patients from Egypt tend to live in rural areas, suggesting the possibility of an environmental component (Chaher et al., 2012). Patients in Egypt also present with a longer duration of symptoms prior to diagnosis of IBC. 28%
of all breast cancer patients in Egypt report seeking medical care no less than 6 months after the initial observation of a breast mass (Lo et al., 2008). This delayed time in seeking treatment could help to explain the increased breast cancer mortality in Egypt. There is no significant difference between patients in Egypt and the U.S. with regard to their menopausal statuses at diagnosis, molecular subtype of the disease, parity, or lymph node involvement, which are all important characteristics in the development of IBC (Lo et al., 2008).

Breast cancer is the most common cancer and the leading cause of death among women in Italy. IBC represents 0.6-2% of all breast cancer cases diagnosed in Italy, with 200-800 new cases diagnosed per year. There is a higher incidence of non-IBC breast cancer in northern Italy compared with southern Italy. This reflects an increase in screening programs for women ages 50-69 in northern Italy, which covers 80% of the population (Ionata et al., 2010). Reductions in non-IBC mortality rates, however, have also been seen in all of Italy. This could be due to the increase in screening programs and in total expenditure on health care, including high-cost technologies and anticancer drugs (Ionata et al., 2010).

By comparing IBC and non-IBC in Italy, the aggressiveness and unique characteristics of the disease are more evident. The incidence of IBC patients diagnosed younger than 44 years of age is 32%, versus 27% for non-IBC. IBC patients in Italy have a greater percentage of ER- negative, PR- negative, HER2- positive, or triple negative cancer compared with non-IBC breast cancer (Ionata et al., 2010). Non-IBC patients in Italy displayed a higher rate of a 10-year disease free survival (DFS) compared with IBC.
patients, 47.1% versus 37.2%, respectively (Ionata et al., 2010). These trends of early age of onset and shorter DFS are similar to what is seen in other countries and consistent with the pathophysiology of IBC.

It is important to note that disparities in the U.S. are also seen among lower education levels and socioeconomic statuses; similar to what is seen in Tunisia and Egypt. Lower SES could result in less access to medical care or the inability to afford medical care. Additionally it may also lead to increased BMI due to lack of affordable nutritional options, and increased comorbidities arising from complications of a high BMI, other health problems, or the lack of affordable healthcare (Andic et al., 2011). Overall, IBC risk decreases with increasing education level (Schairer et al., 2013). A lower education level has been to be correlated to increased duration of breastfeeding, another possible risk factor of IBC (Lê et al., 2006).

**Obesity**

Obesity is a risk factor for developing non-IBC breast cancer in postmenopausal women and is further associated with adverse outcomes. In premenopausal women, however, obesity has not clearly been shown to place women at an increased risk for developing non-IBC breast cancer (Loi et al., 2005). One possible reason for the increased risk of breast cancer in postmenopausal obese patients is the increased levels of estrogen due to peripheral aromatase activity in the adipose tissue. This effect is not as prominent in premenopausal women because their ovaries are responsible for the majority of the endogenous estrogen production (Loi et al., 2005). If increased estrogen
in postmenopausal obese women contributes to poorer survival, this effect would be stronger in ER-positive patients. It was shown, however, that obesity was a significant predictor of outcome in both hormone receptor positive and negative cancer. This suggests that an increased body mass index (BMI), defined as kg/m\(^2\), has additional influences, apart from increased estrogen, that are responsible for its effect on prognosis (Loi et al., 2005). Obese women, for example, may have worse survival outcomes because of comorbidities, such as diabetes or hypertension, associated with obesity, which, in turn, may result in physician modification of the prescribed dose of chemotherapy (Loi et al., 2005).

Non-IBC breast cancer patients with diabetes mellitus, for example, were shown to have worse survival outcomes than non-diabetic patients. One of the main risk factors for type 2 diabetes is obesity. It is possible that the high levels of insulin due to insulin resistance in type 2 diabetes are mitogenic for breast cancer cells. Type 2 diabetes is an independent predictor of survival outcomes in patients at all stages of breast cancer. Furthermore, obese and overweight diabetic patients have a worse survival than non-diabetic patients with the same stage of breast cancer (Yerrabothala et al., 2013).

Among IBC patients, a high BMI was associated with an increased risk for developing IBC, independent from a woman’s menopausal status at diagnosis (Chang et al., 1998). Postmenopausal IBC patients, however, with a higher BMI have worse outcomes when compared with leaner postmenopausal patients (Figure 3) (Change et al., 2000). This could be explained by factors related to obesity that influence survival in IBC patients more strongly when the concentrations of reproductive hormones are low, as
they are after menopause. Overall, however, IBC patients have a significantly higher BMI compared with non-IBC patients, and patients with other cancer in general, despite menopausal status (Chang et al., 1998).

Other factors related to an increased BMI may also play a role in causing obese women to be at an increased risk for IBC. Insulin-like growth factor 1 and dihydroepiandrosterone, for example, are related to obesity and are involved in carcinogenesis. Other hormones and growth factors related to obesity may also be involved in rapid proliferation of malignant cells leading to carcinogenesis (Chang et al., 1998). It is important to note that measuring BMI at the time of IBC diagnosis reflects the actual body size of the patient during the onset and proliferation of the disease because it is a disease with a short duration of development (Chang et al., 1998).
Figure 3: Survival curves of postmenopausal IBC patients by obesity status. Obese and non-obese postmenopausal IBC patients plotted for survival in months and adjusted for other prognostic factors (Figure taken from Chang et al., 2000).
Obesity could also help to explain incidence rates in countries other than the United States. The CDC defines normal individuals as having a BMI less than 24.9, overweight individuals as having a BMI between 25.0 and 29.9 and obese individuals as having a BMI of 30 or higher (CDC, 2012). In Tunisia, the rate of obesity in adults is as high as 50% (Labidi et al., 2008). In contrast, 35.7% of adults in the U.S. are obese (CDC, 2012). The high rate of obesity in Tunisia, for example, could contribute to the high incidence of IBC in that country (Labidi et al., 2008). When comparing IBC patients in Japan to those in the United States, BMI differences also exist. IBC accounts for 0.09-2.9% of all breast cancers in Japan (Natori et al., 2013). In one study, the mean BMI of IBC patients at M.D. Anderson Cancer Center in San Antonio, Texas was 30.9 while the mean BMI of IBC patients at St. Luke’s International Hospital in Tokyo, Japan was 22.5 (Natori et al., 2013). Additionally, the mean BMI of the Japanese women and U.S. women in 2008 were 22.4 and 27.3, respectively. These statistics show that IBC patients at M.D. Anderson Cancer Center have significantly higher BMI’s than the general U.S. population of women while Japanese IBC patients and the general Japanese population of women were similar – further supporting the hypothesis that BMI is a risk factor for patients in the U.S., whereas there may be different epidemiologic factors associated with IBC in patients in Japan (Natori et al., 2013). Further analyses showed that Asian women with IBC, living in Asian countries, had an overall better prognosis compared with Caucasian or African American IBC patients in the U.S. (Natori et al., 2013). These differences could be due to biological factors other than ethnicity, which in Japan, for example, is an ethnically homogenous population, differing from the U.S. where many
individuals are ethnically diverse (Natori et al., 2013). Perhaps the Asian ethnicity is biologically protective. These differences in IBC prognosis could also be caused by environmental factors, such as specific pollutants, which may be more common in the U.S. Finally, lifestyle factors, such as differences in diet and nutrition between the U.S. and Japan, may cause the BMI discrepancy among patient populations.

**Menopausal Status**

A late age of menopause is associated with an increased risk of non-IBC breast cancer. Older premenopausal women are therefore at a higher risk of developing breast cancer compared to postmenopausal women at the same age (Key et al., 2001). Unlike non-IBC breast cancer, IBC incidence increases rapidly until 50 years of age and then begins to plateau (Figure 1) (Hirko et al., 2013). IBC patients are more likely to be diagnosed when premenopausal compared to non-IBC LABC patients; 29.5% of IBC patients are diagnosed when premenopausal compared to 22.2% of non-IBC LABC patients (Schairer et al., 2013). Premenopausal IBC patients have a worse prognosis overall compared to postmenopausal patients (Chang et al., 2000). Premenopausal women are more likely to have ER-/PR- negative IBC; this is consistent with factors associated worse overall survival outcomes. Additionally, when compared to Caucasians, all other racial groups are also more likely to be diagnosed with IBC when premenopausal (Hirko et al., 2013).

It is interesting to note that among IBC patients, premenopausal women have different risk factors compared with postmenopausal women. In Tunisia, for example,
rural residency, pregnancy, and increased number of live births were all risk factors for developing IBC among premenopausal women. This suggests that the increased risk of breast cancer in premenopausal women could be due to a hormonal influence that contributes enhanced cancer development (Mourali et al., 1980).

Premenopausal cases of IBC are more likely to be ER-/PR-negative. Hispanics and American Indian/Alaskan Natives have the highest percentages of patients diagnosed with IBC in the premenopausal years (Hirko et al., 2013). It has also been shown that premenopausal African American women more commonly have triple negative disease, both for IBC and non-IBC, than postmenopausal African American women (Andic et al., 2011). The difference in menopausal status at the time of IBC diagnosis among races could potentially be explained by differences in reproductive factors and lifestyle characteristics. ER-positive and PR-positive disease displays a more favorable survival because of its response to hormonal therapies. Interestingly, postmenopausal patients no longer produce estrogen from their ovaries, but produce it peripherally in their adipose tissue. Therefore, it may be important to consider the patients’ weight because obese postmenopausal patients will have more adipose tissue than non-obese patients and this may be an important factor in treating ER-positive and PR-positive women (Britton et al., 2002).

*Age of Menarche, Pregnancy and Breast Feeding*

Additional risk factors correlated with IBC include: a younger age of menarche, a younger age of first live birth, and a long duration of breast-feeding exceeding 24 months.
(Hirko et al., 2013; Chang et al., 1998). These potential risk factors could help explain some of the racial and geographic disparities among IBC patients. Women in Tunisia, for example, tend to be younger at their age of first pregnancy (Boussen et al., 2010). In one study, 14 out of 15 premenopausal IBC patients had their first child before the age of 18 years (Woodward et al., 2009). IBC patients and non-IBC patients with aggressive breast cancer were 3 times more likely to have their first child before the age of 20 years compared with women diagnosed with nonaggressive breast cancer (Levine et al., 2004). Furthermore, a later age of first live birth was associated with a reduced risk of ER-negative IBC (Schairer et al., 2013).

Tunisian women also have a longer duration of breast-feeding. The mean duration of breast-feeding was 5 months for European women and 28 months for non-European women. The mean duration of breast-feeding was 4 months for patients with an education level of 11 years or more and 8 months for patients with a lower education level. It was 3 months in patients with a BMI less than 25 and 15 months in patients with a BMI greater than 25 (Lê et al., 2006). It is interesting to note that the geographic origin (non-Western countries), education level (low level) and BMI (obese or overweight) all correlate with a longer duration of breast-feeding. This suggests that a combination of lifestyle factors work together to put women at an increased risk for developing IBC.

It has been suggested that IBC is more common during pregnancy (Bonnier et al., 1997). In addition, women who are pregnant and breast-feeding during the time of presentation of breast cancer detection had an increased likelihood of having positive PEV (poussée evolutive, a French classification with clinical features similar to IBC)
Overall, breast cancer is generally thought to be exacerbated by pregnancy because of increased hormonal factors. Premenopausal, pregnant IBC patients have a worse overall survival compared with similar IBC patients who were not pregnant. Furthermore, one case-control study showed that the prevalence of IBC was higher among a pregnant group than a non-pregnant group. The hormonal and immunologic changes associated with pregnancy could enhance breast cancer growth and progression. Additionally, pregnancy is associated in a delay in diagnosis of breast cancer, both IBC and non-IBC breast cancer, resulting in a poorer outcome (Labidi et al., 2008).

First-Degree Family History and High Mammographic Breast Density

In both non-IBC breast cancer and non-IBC LABC, a first-degree family history of breast cancer, defined as having a mother, sister, or daughter with a history of the disease, is associated with an increased risk of developing breast cancer (Schairer et al., 2013). Women with a first-degree family history of breast cancer are also at an increased risk for IBC. This could be due to shared environmental and genetic factors (Tyrer et al., 2004). Individuals with an affected first-degree relative are at a two-fold risk for developing all subtypes of breast cancer. Those with an affected second-degree relative, defined as having an aunt, maternal, or paternal grandmother with a history of breast cancer, have a smaller increase in risk. Not surprisingly, breast cancer has been shown to cluster in families. Additionally, individuals are at a greater risk of developing breast cancer if they carry specific inherited genetic mutations. Germline mutations in the genes BRCA1 and BRCA2 are just two examples of mutations that can predispose an individual
to breast cancer (Key et al., 2001). In contrast, there are no known genetic mutations that predispose a woman to IBC; the risk of IBC is associated with the general inherited risk of breast cancer. Similarly, having a higher mammographic density is associated with an increased risk for developing non-IBC breast cancer. Although women with IBC have a higher breast density as a result of the cancer, there is no correlation between increased breast density and the development of IBC as there is in non-IBC breast cancer.

**Additional Risk Factors**

So much is unknown about the etiology of IBC. Consequently, there may be other risk factors that could contribute to developing IBC, but have not yet been thoroughly studied. The mouse mammary tumor virus (MMTV) is a virus involved in mouse mammary carcinogenesis. MMTV-like sequences have been seen in some breast cancer samples, but are not present in normal tissues. Viral particles of a retrovirus were found in 60% of the breast milk from women with a history of non-IBC breast cancer and in only 5% of the breast milk from women with no breast cancer history (Pogo et al., 2010). Researchers also found that 38% of breast cancer samples from the U.S. contained the *env* gene sequences, which is a protein associated with MMTV. These sequences were 95-99% homologous to MMTV. There were differences in the geographic distributions of the *env* gene sequence-positive breast cancer with the highest prevalence seen in Tunisia, which also has the highest incidence of IBC. This led researchers to investigate IBC samples in the U.S. (Pogo et al., 2010). IBC samples from North America showed a 71% presence of MMTV-related viral sequences compared to 40% in non-IBC controls. These
MMTV viral sequences were seen to be correlated with p53 expression and were most often present in invasive cancers as opposed to in situ carcinomas. These viral sequences could therefore relate to tumor aggressiveness and high tumor grade, suggesting a potential association with the etiology of IBC (Pogo et al., 2010).

Environmental contributions to the development of IBC have not been well defined. One study was performed on a cluster of three women who all developed IBC in a work office within one year. This suggested a link between IBC and the workplace environment (Duke et al., 2010). Another study evaluated an IBC cluster in the Harris and Galveston counties of Texas. Although this study encountered difficulties, it did point out the importance in studying environmental exposures to determine etiologic agents of IBC (Minaei et al., 2012). Exposure to organochlorines, for example, has been shown to elicit responses that may mimic or antagonize the effects of endogenous sex hormones. This could contribute to the growth of aggressive breast cancers such as IBC (Duke et al., 2010).

The biological mechanism of IBC is something that is not fully understood. Statins, which are used to lower cholesterol, have anti-inflammatory properties and may also have anti-tumor effects. Many preclinical studies have shown that statins may suppress the metastatic potential in breast cancer. Certain statins have been shown to reduce the risk of primary IBC or reduce the risk of recurrence of IBC. H-Statins (hydrophilic statins), for example, were associated with a greater progression free survival in IBC patients. This could be due to statins blocking a step involved in the initiation of metastasis and the epithelial-mesenchymal transition. It is important to note,
however, that those patients on statins may also have better access to healthcare or higher education levels, which may also impact survival (Brewer et al., 2013). All of these viral, genetic and environmental risk factors associated with the development of IBC are prime targets further research in order to enhance a greater understanding of the disease.
METHODS

Design and Approval

This study utilized clinical data from a retrospective analysis of 275 patients with the diagnosis of inflammatory breast cancer seen at Dana Farber Cancer Institute (DFCI) and Brigham and Women’s Hospital (BWH) in Boston, MA. This study was approved by the Dana Farber/ Harvard Cancer Center (DF/HCC) Institutional Review Board (IRB) and background data was requested from CORIS between the years of 1997-2012. Data was collected and stored in a password-protected database. The source of this data was collected through the CORIS/CRIS system and confirmed through the electronic medical record system, LMR. Data was stored for analyses through the Harvard Medical School REDCap Program. The principle investigator (PI) for this study was Beth Overmoyer, MD. Co-investigators include, Jennifer Bellon, MD, Laura Warren, MD, Diana Caragancianu, MD, Eren Yeh, MD, Faina Nakhlis, MD, and Heather Jacene, MD.

Sample

Patients in this sample had a histologic or cytologic confirmed invasive breast cancer. They met the clinical characteristics of IBC, tumor stage T4d, with or without detection of lymphatic involvement (NX). They may have had evidence of metastatic disease. Patients were 18 years or older to be included in the study. Some of the data collected included: demographic data, breast cancer characteristics, treatment history, clinical and pathologic disease response to pre-operative chemotherapy, recurrent and
metastatic disease history, and other clinical information that may be important in the future.

**Data Analysis Plan**

A literature review was conducted in order to understand the nature of IBC, including symptoms, clinical diagnosis, molecular profile, and general epidemiology. This allowed for an understanding of what risk factors of IBC have consistently been studied as well as other potential risk factors that may contribute to the development of this disease. This was an important initial step in determining what characteristics to focus on in the DFCI IBC patient population.

Using the patient database, Chi-square and Fisher’s exact tests were performed to determine any statistically significant risk factors in the population and help narrow the focus of this study. Descriptive statistics were compiled to summarize demographic data (age at initial diagnosis, menopausal status, BMI, comorbidities, smoking history, duration of symptoms, race/ethnicity, family history, and genetic predispositions), breast cancer characteristics (stage, hormonal receptor status, HER2 status) and recurrent and metastatic information (date of diagnosis, recurrence and progression, locoregional recurrence, distant recurrence, whether the patient had metastatic disease at presentation and the location of the metastases).

When analyzing race, only Caucasian and African American patients were studied because they provided the most abundant data source. There were very few patients who fell into the categories of Asian, Hispanic, and unknown. Premenopausal and perimenopausal women were also combined in this analysis and compared with
postmenopausal patients. When analyzing comorbidities, diabetes became a focus because of the correlation between type 2 diabetes and BMI. The determination of overweight and obese statuses for patients utilized a BMI of <25, 25-29.9 and >= 30, respectively, following the CDC’s definitions. Age was calculated for each patient using her date of birth. Season of diagnosis was calculated using the patient’s date of diagnosis. Fall was considered to be September 21st – December 20th, winter was considered to be December 21st – March 20th; spring was considered to be March 21st – June 20th; summer was considered to be June 21st – September 20th. The goal of this study was to use an epidemiologic analysis of patients with inflammatory breast cancer treated at DFCI in attempt to elucidate risk factors for this rare disease.
RESULTS

Chi-square and Fisher’s exact tests were performed to determine statistical significance of risk factors in the DFCI IBC patient database. The following summarizes the association between specific risk factors and the development of IBC using a statistical significance of p<0.05.

In summary, African American patients with IBC were more likely to have diabetes than Caucasian patients. Postmenopausal women were more likely to have a history of smoking, hyperlipidemia, hypertension, or another comorbidities compared with premenopausal women. Patients with ER- positive and/or PR- positive IBC were more likely to have a history of smoking. Patients with a positive family history of breast cancer were more likely to also have a positive family history of ovarian cancer. Patients with a family history of breast cancer were more likely to have hyperlipidemia. Patients with a family history of ovarian cancer were more likely to have hypertension. Finally, patients whose IBC recurred or progressed had a greater likelihood of having hypertension, hyperlipidemia, or having presented with metastatic disease at the time of diagnosis.

DEMOGRAPHIC CHARACTERISTICS

Race and Menopausal Status

A total of 275 patients were analyzed. 83% of patients were Caucasian, 5% were African American, 2% were Asian, 1% were Hispanic, 2% were “other,” and 7% were
unknown for race (Figure 4). The mean age of diagnosis was 50.5 years of age for Caucasian women and 53 years of age for African American women.

273 patients were analyzed for menopausal status (2 patients in the database were unknown or unrecorded for menopausal status). 55% of women were premenopausal when diagnosed and 45% were postmenopausal when diagnosed (Figure 4).
Figure 4: Race and menopausal status. Percentage of patients with each of the following demographic characteristics: A.) Caucasian or African American; B.) premenopausal or postmenopausal at diagnosis.
Family History

There is no known genetic predisposition for the development of IBC. Therefore, family history of breast (IBC or non-IBC) and ovarian cancer was analyzed to determine if any hereditary pattern existed. The majority of DFCI IBC patients did not have a family history of breast or ovarian cancer. For breast cancer, 21% of patients had a first-degree relative with breast cancer, of which 8% had a sister with a history of the disease and 13% had a mother with a history of the disease. 30% had a second-degree relative with breast cancer, of which 23% had a maternal or paternal aunt with a history of disease and 7% had a maternal grandmother with a history of the disease. Only 4% of patients had a first-degree relative with a history of ovarian cancer, 1% had a sister with a history of ovarian and 3% had a mother with a history of the ovarian cancer. Finally, 5% of patients had a second-degree relative with a history of ovarian cancer, of which 4% had a maternal or paternal aunt with ovarian cancer and 1% had a maternal grandmother with ovarian cancer (Figure 5).
Figure 5: Family history. Percentage of IBC patients with a family history of: A.) breast cancer in a first-degree relative; B.) breast cancer in a second-degree relative; C.) ovarian cancer in a first degree relative; D.) ovarian cancer in a second-degree relative.
Genetic Predispositions

Patients were assessed for a genetic predisposition to breast cancer, namely BRCA1 and BRCA2 mutations. The majority of patients, however, did not have a genetic assessment. 2% of patients were positive and 17% were negative for a BRCA1 mutation; 1% of patients were positive and 17% were negative for a BRCA2 mutation (Figure 6). Since mutations in the BRCA1 and BRCA2 genes are associated with the Hereditary Breast and Ovarian Cancer Syndromes, family history was analyzed for patients who were either positive or negative for BRCA1 or BRCA2 mutations to determine whether a higher percentage BRCA1 or BRCA2 positive versus negative patients had a known family history of breast or ovarian cancer. The percentage of the entire patient population was also analyzed to determine if a substantial number of DFCI IBC patients were BRCA1 or BRCA2 negative and also had a positive family history (Table 2).
Figure 6: Genetic predispositions. Patients were recorded as being: A.) BRCA1 positive; B.) BRCA2 positive.
Table 2: Genetic predisposition and family history. The number and percentage of patients tested for BRCA1 and BRCA2 with a first or second-degree relative with a history of breast or ovarian cancer. 153 patients had a positive family history of breast or ovarian cancer.

<table>
<thead>
<tr>
<th>Patients with family history of breast/ovarian cancer N=153</th>
<th>BRCA1 Positive N=5, (3.3%)</th>
<th>BRCA2 Positive N=2, (1.3%)</th>
<th>BRCA1/BRCA2 negative N=47, (30.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree relative with ovarian cancer</td>
<td>2, (1.3%)</td>
<td>0, (0%)</td>
<td>3, (2.0%)</td>
</tr>
<tr>
<td>First-degree relative with breast cancer</td>
<td>0, (0%)</td>
<td>1, (0.65%)</td>
<td>15, (9.8%)</td>
</tr>
<tr>
<td>Second-degree relative with ovarian cancer</td>
<td>1, (0.65%)</td>
<td>0, (0%)</td>
<td>6, (3.9%)</td>
</tr>
<tr>
<td>Second-degree relative with breast cancer</td>
<td>1, (0.65%)</td>
<td>1, (0.65%)</td>
<td>17, (11.1%)</td>
</tr>
</tbody>
</table>
BMI

Body mass index (BMI) was analyzed to determine if the majority of the DFCI IBC patients were of normal weight, overweight or obese. A BMI of <25 was considered normal, 25-29.9 was considered overweight and \( \geq 30 \) was considered obese. Looking at BMI, 23\% of patients were considered to be of normal weight 35\% were considered overweight, and 42\% were considered obese ; which translates into 77\% of patients having a BMI higher than what is considered normal (Figure 7). Patients who were obese or overweight were more likely to have a history of smoking or to be a smoker at the time of IBC diagnosis, and were more likely have a comorbidity such as hyperlipidemia, diabetes, hypertension, or coronary artery disease. Table 3 summarizes the percentage of patients within each BMI category, who also had a smoking history or co-morbidity. It is important to note that data on BMI was only available for 201 patients in the database.
Figure 7: BMI. Percentage of patients with IBC having a normal (<25), overweight (25-29.9), or obese (≥30) BMI at the time of diagnosis.
Table 3: Trends of association of BMI, smoking status, and comorbidities at time of diagnosis: Percentage of patients within each BMI category, having a smoking history or other comorbidities. The following results are not statistically significant, but smoking status and comorbidities seem to trend with a higher BMI.

<table>
<thead>
<tr>
<th>Smoking Status and Comorbidities at time of Diagnosis</th>
<th>BMI at time of Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (&lt;25)</td>
</tr>
<tr>
<td>Percentage with a history of smoking</td>
<td>31.82%</td>
</tr>
<tr>
<td>Percentage with diabetes</td>
<td>0%</td>
</tr>
<tr>
<td>Percentage with hypertension</td>
<td>16.33%</td>
</tr>
<tr>
<td>Percentage with coronary artery disease</td>
<td>0%</td>
</tr>
<tr>
<td>Percentage with “other” co-morbidity</td>
<td>24.29%</td>
</tr>
</tbody>
</table>
The DFCI IBC patient database was analyzed to determine whether premenopausal or postmenopausal women were more likely to have normal, overweight or obese levels of BMI. The percentage of premenopausal and postmenopausal patients for each BMI category was determined (Table 4).
Table 4: Menopausal status and BMI. The number and percentage of premenopausal and postmenopausal woman with normal, overweight, or obese range BMI. The following results are not statistically significant, but both premenopausal and postmenopausal IBC patients seem to trend towards a higher BMI.

<table>
<thead>
<tr>
<th>BMI</th>
<th>IBC N=215, (78%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td></td>
</tr>
<tr>
<td>&lt;25 (normal)</td>
<td>N=117, (54.4%)</td>
</tr>
<tr>
<td>25-29.9 (overweight)</td>
<td>23, (19.7%)</td>
</tr>
<tr>
<td>&gt;= 30 (obese)</td>
<td>50, (42.7%)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td></td>
</tr>
<tr>
<td>&lt;25 (normal)</td>
<td>N=98, (45.6%)</td>
</tr>
<tr>
<td>25-29.9 (overweight)</td>
<td>32, (32.7%)</td>
</tr>
<tr>
<td>&gt;= 30 (obese)</td>
<td>40, (40.8%)</td>
</tr>
</tbody>
</table>
Comorbidities

The majority of patients did not have a co-morbidity diagnosed at IBC presentation. 9% had hyperlipidemia, 23% had hypertension, 8% had depression, 1% had coronary artery disease and 5% had diabetes (Figure 8). Focusing on the 4% of patients who were diagnosed with diabetes, 78.8% were postmenopausal. Of the 4% of the DFCI IBC patient population that had diabetes at the time of diagnosis, 54.6% of patients recurred or progressed (80% locoregional recurrence and 83.3% distant recurrence) (Table 5). Data in regards to diabetes was recorded for all but 1 patient in this cohort.
**Figure 8: Comorbidities.** Percentage of patients had hyperlipidemia, hypertension, depression, coronary artery disease, or diabetes in the DFCI IBC patient population.
**Table 5: Population of patients with diabetes.** Percentage of IBC patients with diabetes and disease recurrence or progression; distant or locoregional recurrences compared with the total patient population. Non-statistical trend toward higher recurrence rate among IBC patients with diabetes.

<table>
<thead>
<tr>
<th>Recurrence or Progression</th>
<th>Patients with diabetes, N= 11</th>
<th>Total population assessed for diabetes N=179, (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any recurrence or progression</td>
<td>6, (54.6%)</td>
<td>6, (3.4%)</td>
</tr>
<tr>
<td>Locoregional Recurrence</td>
<td>4, (36.4%)</td>
<td>4, (2.2%)</td>
</tr>
<tr>
<td>Distant Recurrence</td>
<td>5, (45.5%)</td>
<td>5, (2.8%)</td>
</tr>
</tbody>
</table>
**Duration of Symptoms**

Patients’ duration of symptoms prior to diagnosis was recorded in 272 patients. The duration of symptoms was recorded as: less than 1 month, between 1-2 months, between 2-4 months, between 4-6 months, and greater than 6 months. 35% of patients presented with a duration of IBC symptoms of less than 1 month, 35% presented with a symptom duration between 1-2 months, 16% presented with a symptom duration between 2-4 months, 6% presented with a symptom duration between 4-6 months, 2% presented with a symptom duration longer than 6 months. 2% had no symptom duration noted (Figure 9).

The mean age of patients was calculated for each category of duration of symptoms. More than 2/3 of patients presented with a duration of less than 1 month or between 1-2 months: 36% and 35%, respectively. The mean age of patients presenting with symptoms of less than 2 months was similar to the DFCI IBC patient population as a whole, 51 years and 49.5 years, respectively. Furthermore, younger patients had proportionally longer durations of symptoms prior to diagnosis. The mean age of patients presenting with a duration of symptoms longer than 6 months prior to diagnosis was 42 years of age, compared with 49.8 years of age for patients presenting with a duration of symptoms less than 6 months prior to diagnosis (Figure 9).
Figure 9: Duration of symptoms at diagnosis for IBC patients. A.) Percentage of patients with various duration of symptoms prior to diagnosis; B.) Mean age of patients for each duration of symptoms category.
Season of Diagnosis

Finally, when looking at the demographic characteristics of IBC patients, the season in which each patient was diagnosed was analyzed. Seasons were determined by the following dates: fall was considered to be September 21st – December 20th; winter was considered to be December 21st – March 20th; spring was considered to be March 21st – June 20th; summer was considered to be June 21st – September 20th. Patients were diagnosed most frequently in the spring, followed by summer, winter, and then fall. 29% of patients were diagnosed in the spring, 28% were diagnosed in the summer, 25% were diagnosed in the winter, and 18% were diagnosed in the fall (Figure 10). Since IBC is such an aggressive disease, associated with the majority of patients having a symptom duration of less than 1 month prior to diagnosis, the season of diagnosis would also correspond to season of onset of IBC. Although intriguing, these results were not statistically significant.
Figure 10: Season of Diagnosis. Percentage of patients who presented with IBC in spring (March 21st – June 20th), summer (June 21st – September 20th), winter (December 21st – March 20th) and fall (September 21st – December 20th).
BREAST CANCER CHARACTERISTICS

Molecular Subtypes

IBC tumor samples were analyzed for ER, PR, and HER2 statuses (positive or negative). 270 samples were analyzed. It was determined that 16% of tumors were HER2-positive and ER-positive (Luminal B), 19% were ER-negative, PR-negative, and HER2-negative (triple negative), 22% were HER2 positive, and 16% were HER2-negative, ER-positive, and/or PR-positive (Luminal A). 4% of patients had tumors for which were unknown for ER status, 4% were unknown for PR status, and 14% were unknown for HER2 status (Figure 11).
Figure 11: Breast cancer subtypes. IBC tumor samples were recorded for being: A.) ER-negative, PR-negative, HER2-negative (triple negative); B.) HER2-negative, ER-positive, and/or PR-positive (Luminal A); C.) HER2-positive and ER-positive (Luminal B); D.) HER2-positive.
METASTATIC DISEASE

264 of the IBC patients had their metastatic status at presentation recorded. 25% of these patients had evidence of metastatic disease upon presentation. The location of the metastases was also recorded. Most of these patients had metastases to the bone, followed by liver, lymph nodes, lung, “other” locations, soft tissue, and 0 had metastases in the central nervous system at presentation (CNS) (Figure 12).
Figure 12: Metastatic status at time of presentation and location of metastases. Patients with metastatic disease at presentation: A.) evidence of metastatic disease; B.) “checked” as having a presence of bone metastasis, “unchecked” as having an absence of bone metastasis; C.) “checked” as having a presence of liver metastasis, “unchecked” as having an absence of liver metastasis
Figure 12 (continued): Metastatic status at time of presentation and location of metastases. Patients with metastatic disease at presentation: D.) “checked” as having a presence of lymph node metastasis, “unchecked” as having an absence lymph node metastasis; E.) “checked” as having a presence of lung metastasis, “unchecked” as having an absence of lung metastasis; F.) “checked” as having a presence of metastasis in another location, “unchecked” as having an absence of metastasis in another location; and G.) “checked” as having a presence of soft tissue metastasis, “unchecked” as having an absence of soft tissue metastasis
Additionally, hormone receptor composition was analyzed for those patients who had metastatic disease on presentation. Patients who had HER2 overexpressing cancer were more likely to have metastatic involvement on presentation, followed by luminal A, and luminal B and triple negative disease. The percentages of DFCI IBC patients who had both metastatic disease upon presentation and had a specific receptor composition were analyzed in order to evaluate trends in the population (Table 6).
Table 6: Receptor composition of the primary IBC tumor among patients who presented with metastatic disease. Percentage of patients with metastatic disease for each hormone receptor and HER2 composition.

<table>
<thead>
<tr>
<th>Hormone Receptor and HER2 Composition</th>
<th>Percentage of Patients with Metastatic Disease N=64, (25%)</th>
<th>Percentage of Total Patient Population N=261</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>12, (18.8%)</td>
<td>12, (4.6%)</td>
</tr>
<tr>
<td>Luminal B</td>
<td>11, (17.2%)</td>
<td>11, (4.2%)</td>
</tr>
<tr>
<td>HER2- Overexpressing</td>
<td>15, (23.4%)</td>
<td>15, (5.8)%</td>
</tr>
<tr>
<td>Triple Negative</td>
<td>11, (17.2%)</td>
<td>11, (4.2%)</td>
</tr>
</tbody>
</table>
DISCUSSION

The purpose of this study was to evaluate the major risk factors of developing IBC in order to gain a better understanding of the cause of this aggressive and rare disease. This study demonstrated various trends in a single study population of IBC patients referred to Dana Farber Cancer Institute, which enabled us to hypothesize about the epidemiology of IBC as a whole. Chi Square and Fisher’s Exact tests allowed us to narrow our focus on risk factors that may have been most important in the development of IBC. Our findings, however, were primarily based on the descriptive statistics performed on the study population from Dana Farber Cancer Institute in Boston, MA. These data were not statistically significant, but displayed key trends among one particular IBC patient population.

As shown in our results, the majority of IBC patients in the DFCI database were Caucasian (Figure 4). Therefore, although it was determined that the mean age of diagnosis in Caucasians was in fact younger than in African American patients, this is not consistent with the literature (Anderson et al., 2005-2006; Overmoyer et al., in press). Age of diagnosis was not considered to be an important trend or observation in our study due to the homogenous nature of the DFCI patient population; it was not representative of the U.S. population as a whole.

We observed that patients were more likely to be diagnosed when premenopausal, which is a trend that is consistent with the literature (Figure 4) (Hance et al. 2005; Labidi et al., 2008). Unlike other studies, we chose not to focus on the differences in menopausal status among racial groups because we did not have a significant number of African
American, Asian or Hispanic patients compared to the number of Caucasian patients in our study.

Each of the following four subtypes of breast cancer were present in our patient population: ER-negative, PR-negative, HER2-negative (triple negative); HER2-negative and ER-positive and/or PR-positive (Luminal A); HER2-positive and ER-positive (Luminal B); and HER2 overexpressing. Van Laere et al. noted that all molecular subtypes found in non-IBC were also detectable in IBC, which is consistent with our results. Furthermore, Van Laere et al. noted that the specific molecular subtypes found in non-IBC occurred at a different frequency in IBC patients. His analysis demonstrated a higher percentage of IBC patients had HER2-positive disease versus non-IBC patients, 22% and 9%, respectively and a lower percentage of IBC patients had Luminal A subtype versus non-IBC patients, 19% and 42%, respectively (Van Laere et al., 2013). Unlike patients the Van Laere study, patients from DFCI were most likely to have Luminal A subtype, followed by HER2 overexpressing, triple negative, and finally, Luminal B. This was an interesting trend because studies have shown that IBC typically displays a highly proliferative molecular subtype, such as triple negative (Overmoyer et al., in press). The lack of a robust percentage of highly proliferative subtypes in the DFCI IBC patient population may be due to the large percentage of patients who did not have tumors, assessed for hormonal and HER2 status, 17% (Figure 11). This indicates that more women in the DFCI IBC patient population may have triple negative or HER2-positive disease but were not tested for hormonal or HER2 status. Additionally, our disease variation compared with Van Laere’s study, could be due to selection bias.
Patients who present with symptoms of IBC and have Luminal A disease may be more likely to be referred to DFCI. In contrast, patients who present with symptoms of IBC and who have a highly proliferative subtype, such as triple negative, may cause physicians to prescribe treatment immediately, and are therefore not referred to DFCI.

The trends in the metastatic presentation of IBC at DFCI were consistent with what has been seen in other patient populations. 25% of DFCI IBC patients presented with metastatic disease (Figure 12). According to the literature, 20-40% of IBC patients have metastases in distant organs upon presentation (Kleer et al., 2000). Patients were found to have metastases most frequently in the bone, followed by liver, distant lymph nodes, lung, and soft tissue; whereas no one presented with CNS metastases (Figure 12). The patients who had disease that was HER2- overexpressing had the highest percentage of metastatic disease upon presentation, followed by Luminal A, triple negative, and Luminal B (Table 6). This pattern seems consistent with the biology of hormone receptor positive disease (Luminal A, Luminal B) which is more indolent, having less metastatic potential.

IBC patients at DFCI were more likely to test negative for the genes BRCA1 and BRCA2, if they were tested at all (Figure 6). These two genes are known to predispose an individual to breast and ovarian cancer, in general (Key et al., 2001). There are no defined inherited genetic predispositions specifically for IBC. This led us to look at the relationship between patients who tested negative for either of these genes and their family histories of breast and ovarian cancer to see if an association of family history might suggest another inherited genetic profile that is different from BRCA1 or BRCA2.
Although the majority of patients lack a family history of breast or ovarian cancer in this patient population, there are still a significant percentage of patients who have a family history of breast cancer. 21% of patients had a first degree relative with a history of breast cancer (8% and 13% had a sister and mother with a history of breast, respectively) (Figure 5). We believe that these statistics may indicate an important hereditary predisposition to the development of IBC, which needs to be determined with further investigation.

A high percentage of \textit{BRCA1} and \textit{BRCA2} positive patients also had a family history of ovarian cancer as well as breast cancer. Interestingly, however, a larger percentage of the entire DFCI IBC patient population were composed of patients who tested negative for \textit{BRCA1} or \textit{BRCA2}, but also had a family history of breast or ovarian cancer. Between 5-7% of \textit{BRCA1} or \textit{BRCA2} negative IBC patients from DFCI, for example, have a first- or second-degree relative with breast cancer (Table 2). This could suggest an additional genetic predisposition or determinant other than \textit{BRCA1} and \textit{BRCA2}, which may be associated with an increased risk specifically for developing IBC. Models such as BRACPro or the IBIS Model calculate the likelihood of carrying the \textit{BRCA1} or \textit{BRCA2} genes based upon factors such as having first- or second-degree relatives with breast cancer, age of menarche, BMI, and age of first live birth (Gail et al., 2010). BRCAPro was used to calculate the probability of women carrying a \textit{BRCA} gene mutation by assessing women who were prescreened and selected for \textit{BRCA} gene sequence based on their breast cancer family history. A family history of early onset of breast cancer, bilateral breast cancer, and both breast and ovarian cancer suggested an
inherited breast and ovarian cancer predisposition (Euhus et al., 2002). A second breast cancer prediction model, the IBIS Model, also incorporates family history of breast cancer to determine the likelihood of carrying a genetic predisposition to breast cancer. \(BRCA1\) and \(BRCA2\) only account for 5% of breast cancer, therefore researchers speculate that there must be other lower risk susceptibility genes that explain the familial aggregation of breast cancer (Tyrer et al., 2004). Therefore, we hypothesize that the existence of a large percentage of patients with first- or second-degree relatives with breast cancer among our IBC population at DFCI could indicate an additional genetic risk for IBC.

IBC patients typically present with an aggressive disease after having a duration of symptoms lasting no longer than 6 months. Most patients, in fact, present after having a duration of symptoms equaling less than 3 months (Figure 9) (Anderson et al., 2005-2006; Wingo et al., 2004). We researched the duration of symptoms prior to presentation among the DFCI IBC patients. The DFCI IBC patients were more likely to present with symptoms lasting less than 2 months. These patients who presented with duration of symptoms lasting less than 2 months had a mean age of diagnosis similar to that of the mean age of the DFCI IBC patient population as a whole, 51 years and 49.5 years, respectively. Although the mean age of our population is younger than the mean age of 57 years seen in IBC patients in the U.S., it does fall within the range of patients typically presenting with IBC, which is 45-57 years of age (Anderson et al., 2005-2006; Overmoyer et al., in press). By further studying the duration of symptoms of IBC patients, we noted a striking trend – a longer duration of symptoms prior to diagnosis was
seen in younger patients (Figure 9). This suggests a delay in diagnosis due to age alone. Patients presenting with a duration of symptoms of >6 months, for example, had a mean age of 42 years, which is much younger than the mean age of 49.8 years among DFCI IBC patients presenting with a duration of symptoms of less than 6 months, as well as the IBC patients in the U.S. population as a whole.

We hypothesized that those patients presenting with symptoms longer than 4 months may have characteristics or risk factors that set them apart from other IBC patients. 21.7% of our patients presenting with a longer duration of symptoms prior to diagnosis had hyperlipidemia and 26.2% had hypertension. This is interesting because only 9% of the entire DFCI IBC patient population had hyperlipidemia (Figure 8). The high rate of hyperlipidemia and hypertension in these patients could be due to a high BMI, a known risk factor for developing IBC. Further discussion of the role of BMI in IBC will follow. The comorbidity status in these patients suggests that they were under a physician’s care, not due to a lack of access to care that caused their delay in diagnosis. The lack of awareness of IBC and its risk factors further emphasizes the importance of increasing investigation and research of the disease.

Patients in the DFCI IBC population displayed a temporal trend in time of presentation, therefore suggesting a seasonal component of the disease. Patients were more likely to be diagnosed in the spring, followed by summer, winter, and fall (Figure 10). A study by Oh et al. has shown that non-IBC breast cancer peaks during the months of spring. Researchers suggested that melatonin, a chemical messenger activated by darkness, might provide a protective effect during the winter months when there is less
sunlight. Additionally, Vitamin D levels, which directly correlate with sunlight and are highest in the summer, have been seen to inversely correlate with breast cancer incidence (Oh et al., 2010). Oh et al. also noted that seasonal effects increase as the population becomes further from equator (more Northern climates), which is consistent with our particular patient population in Boston, MA.

When focusing on younger patients who have a longer time to presentation (>4 months), we found that 43.5% of these patients tend to present during the winter months, while patients with shorter duration of symptoms prior to presentation are evenly distributed throughout all seasons. Although these patients tend to present in the winter, they may still have developed IBC in the warmer seasons, but exhibited because of a delay in diagnosis.

We hypothesized that there is a seasonal component that is associated with an increased risk of developing IBC. This could relate to an infectious component for the development IBC. People are more likely to have influenza and allergic rhinitis during certain times of the year, such as the spring (Oh et al., 2010). It is possible that there could be a viral component to IBC. Infection by viruses, similar to MMTV, could play a role in the pathophysiology of IBC and warrants further investigation. Furthermore, the weather differences between seasons in Boston, MA are drastic. The seasonal component could be due to clothing differences worn among the different seasons. The heavy clothes worn during winter, for example, may affect self-examination of women, therefore altering when they first present.
Obesity has been shown to be associated with an increased risk for developing IBC. Unlike non-IBC breast cancer, overweight or obese women who are either premenopausal or postmenopausal women are at an increased risk for developing IBC. This contrasts with non-IBC breast cancer, where only postmenopausal obese or overweight women are at an increased risk (Chang et al., 2000; Loi et al., 2005). Our data was consistent with the literature; an increased BMI was associated with an increased risk of developing IBC, with 77% of patients having an overweight (25-29.9) or obese (>=30) BMI (Figure 7). This is significantly greater than the 69.2% of the U.S. population that is overweight or obese (CDC, 2012). Obese DFCI IBC patients were more likely to be premenopausal than postmenopausal; this is also consistent with IBC patient data seen in the literature (Table 4). Furthermore, the DFCI IBC patients who were obese or overweight were more likely to have a history of smoking or be smokers at the time of IBC presentation, and have other comorbidities such as, hyperlipidemia, diabetes, hypertension, or coronary artery disease (Table 3). The combination of a high BMI, presence of a comorbidity as a result of having a high BMI, and lifestyle choices, such as smoking, seem to be important risk factors in developing IBC. We hypothesize, therefore, that these major risk factors of IBC are either the result of lifestyle factors that can be modified or may each independently contribute to the etiology of developing the disease. Having a high BMI, for example, can lead to the development of many comorbidities. Altering diet, nutrition, and exercise could be significant in reducing the risk of developing IBC.
Since a large percentage of DFCI IBC patients were overweight or obese, we decided to focus on an associated comorbidity such as diabetes. A high BMI is a risk factor for Type 2 diabetes mellitus, a disease that has been implicated in adversely affecting the outcomes of all cancer patients, including breast cancer patients (Yerrabothala et al., 2013). Studies have shown that hyperinsulinemia as a result of Type 2 diabetes leads to higher levels insulin-like growth factor-I (IGF-I). IGF-I can exert a mitogenic effect on breast epithelial tissue and contribute to the development of breast cancer (Dalamaga et al., 2013). While only 4% of patients with IBC in our database had diabetes, they were at an increased risk for adverse survival (Figure 8). These patients were more likely to experience disease recurrence or progression (locoregional or distant) (Table 5). Diabetes has been shown to negatively affect survival time of breast cancer patients, which is consistent with our results for DFCI IBC patients (Yerrabothala et al., 2013). We hypothesized that IBC patients with diabetes would have a worse outcome or shorter survival time compared with non-diabetic IBC patients, therefore controlling the diabetes may be associated with a more favorable disease outcome and should be strongly pursued.

Our data displays significant consistencies with the IBC literature such as, involving a greater number of premenopausal women, similar mean age of diagnosis, the presence of all known molecular subtypes, a high percentage of patients presenting with metastatic disease, the overall short duration of symptoms at presentation, and the significantly high BMI relative to the general U.S. population. We have also found unique associations, however, that deserve further study. In summary, we believe that
there could be a hereditary or genetic component as well as a seasonal component to the development of IBC. Additionally, it seems likely that there are modifiable lifestyle factors that can place a woman at a greater risk for developing this disease. These are of extreme importance and would benefit from further study because they point to a lack of awareness of the disease. Patients in the DFCI IBC population who were much younger, for example, displayed a delay in diagnosis as well as increased comorbidities, which may be preventable by increasing knowledge of the risk factors of developing this disease. Overall, women who have a relative with a history of breast cancer or who are overweight or obese are at a greater risk for IBC. Comorbidities, such as diabetes, especially arising in women with IBC and a high BMI, can also be associated with a greater risk of disease recurrence or progression.

There are several limitations of this study including, a small sample size of 275 patients, most of whom were Caucasian. This was a single institution study with a referral base in the North East, therefore limiting diversity. Many of the risk factors studied were not evaluated in all of the patients in our database and were classified as “unknown,” thus hindering our ability to thoroughly evaluate some characteristics of risk factors. Examples include: genetic predispositions, hormone receptor status and HER2 status. Although this evaluation has limitations, its strengths include: substantial data on BMI, comorbidities, family history, season of diagnosis, and duration of symptoms, all of which suggest key associations among the DFCI IBC patients. Our findings and conclusions are important in suggesting trends that may exist in the larger population of IBC patients in the U.S. We hope that the risk factors we have identified as being
important in the development of IBC will help to provide more information about the disease.
BIBLIOGRAPHY


70


44. Robertson, F. M., Bondy, M., Yang, W., Yamauchi, H., Wiggins, S., Kamrudin, S., … Cristofanilli, M. (2010). Inflammatory breast cancer: the disease, the biology, the treatment. CA: a cancer journal for clinicians, 60(6), 351–375. doi:10.3322/caac.20082


VITA

RANDIE E. WHITE

Address: 674 Elm Street
South Dartmouth, MA, 02748
508-813-6767

Email: randiew@bu.edu

Year of Birth: 1990

Education:
Boston College
Bachelor of Science in Biology, May 2012

Boston University School of Medicine, Boston, MA
Candidate for Master of Science of Medical Science, May 2014

Monteverde Institute, Monteverde, Costa Rica
Studied Tropical Science and Sustainability, Summer 2010

Work Experience

02/14 to present Examkrackers, Inc.
Boston, MA
• Instructed students preparing to take the MCAT
• Prepared weekly lessons on biological sciences, organic chemistry, and verbal reasoning to lecture students each week in a classroom setting and administer practice exams, as well as was available for outside help

06/12 to 08/14 Tallman Insurance and Co, Inc.
Taunton, MA
• Managed the front desk of the insurance company, working between clients and agents
• Responsible for money that came through the office, issuing certificates of insurance and insurance binders, as well as general office organization

06/11 to 08/12 Trinity Partners
Waltham, MA
• Worked in pharmaceutical and biotechnology consulting, contributed to primary market research and secondary
research as well as presentation development for different projects and teams
  • Completed an internal project and presentation on health care reform outside of the US and its implications for the success of the pharmaceutical market and life sciences consulting

06/04 to 08/10  Buzzards Sailing School
Pocasset, MA
  • Taught sailing to children ages 8 to 16, responsible for program curriculum, organization of classes and water safety for forty children each class, control and management of junior instructors and staff members
  • Received two instructor awards in 2008 and 2010 for teaching, responsibility and hard work

06/10 to 08/10  Buzzards Sailing School
Pocasset, MA
  • In charge of application forms, medical and liability forms, tuition collection and management, inputting enrollment information into excel to organize individual classes.
  • Contacting parents, and working between parents and staff members.

Medically Relevant/Volunteer Experience

09/13 to present  Dana Farber Cancer Institute
Inflammatory Breast Cancer
Boston, MA
  • Researched the potential risk factors in developing the disease of inflammatory breast cancer by using a patient database of patients seen at Dana Farber Cancer Institute
  • Ran a comprehensive literature review of information on inflammatory breast cancer as well as used statistical software to analyze data from the Dana Farber inflammatory breast cancer patient population

02/11 to 01/12  Brigham and Women’s Hospital
Central Transport Division
Boston, MA
  • Assisted the central transport team with filling and delivering labs, bringing wheelchairs and other medical
items to and from patient floors and helping patients to surgery.

05/09 to 08/09
Falmouth Hospital
Emergency Department
Falmouth, MA
  • Worked between the waiting room and trauma care
  assisting triage nurses, admitting patients, keeping patients