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Breast Cancer in HIV-positive Patients: A Multi-Institutional Retrospective Review

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Abstract

Purpose: The incidence of breast cancer in HIV-positive patients continues to increase as the population ages. There is limited data to support standard screening, diagnosis, or treatment protocols for breast cancer in HIV-positive patients, and current standard of practice guidelines are derived from HIV-negative, non-immunosuppressed patients. Because of the current HIV epidemic and high breast cancer mortality rate, we compared the characteristics of a unique population of HIV-positive women in the Baltimore-Washington, D.C. area with breast cancer.

Patients and Methods: This study analyzed all breast cancer diagnoses in HIV-positive patients (N=43) from January 1, 2004 - December 31, 2014 at four hospitals in the Baltimore-Washington, D.C. area. Demographic comparisons were conducted using Fisher's Exact test for categorical variables and t-tests for continuous variables.

Results: The average age in years at breast cancer diagnosis was significantly lower in HIV positive individuals than the control (53 vs. 60, p=0.009). A significant difference was found in hormone receptor status for luminal B (ER+/PR-/HER2-), HER2 enriched (ER-/PR-/HER2+), and basal types (triple negative ER-/PR-/HER2-), p=0.04, p=0.009, and p=0.002 respectively. However, no significant differences were found when comparing stage at diagnosis (p=0.31). Chemotherapy was the only treatment administered at a statistically higher rate to HIV-positive patients when compared to the control (p=0.02).

Conclusions: In this small demographic study, HIV-positive breast cancer patients presented at a younger age, not unlike findings suggested in other large analyses of non-AIDS-defining cancers in similar patient populations. This study further highlights the need for future research of breast cancer in HIV-positive patients to help guide preventive care guidelines for screening and diagnosis of breast cancer.

INTRODUCTION

Over the years, breast cancer incidence has increased in human immunodeficiency virus (HIV)-positive patients, despite breast cancer being a non-AIDS-defining cancer. Several studies attributed this increase in frequency of breast cancer diagnoses in HIV-positive patients to improved HIV therapy or increased surveillance [1,2]. Many studies have demonstrated that HIV-positive patients do not have an increased risk of developing breast cancer; they argue that the incidence of breast cancer is in fact decreased in both male and female HIV positive patients [3,4,5,6,7]. Another study in 2002 argued that the incidence of breast cancer is not greater in HIV patients because breast cancer is not acquired as a result of immunodeficiency [8]. Hence, the National Cancer Institute does not recognize people infected with HIV to have an increased risk of breast cancer.

The known number one risk factor for the development of breast cancer is increased age. HIV-positive patients historically have died younger than non-HIV infected patients, which previously precluded them from developing breast cancers as breast cancer is frequently seen in older populations. Currently, HIV-positive patients are living longer due to highly active antiretroviral therapy and other treatments [9,10]. The incidence of breast cancer in HIV-positive patient continues to increase, as they are more susceptible to develop cancers that are seen in aging populations [11]. Therefore, as can be expected, when the population of surviving HIV-positive patients quadrupled in size over 10 years, breast cancer incidence also increased [12].

Although sample sizes are often small, several studies have recently examined HIV and breast cancer in the United States. A retrospective review from 2002-2010 on 2,060 HIV-positive patients at an outpatient clinic in Louisiana found no difference in presentation, pathologic aggressiveness, or survival among HIV-positive breast cancer patients [13]. Other studies have closely examined the relationship between treatment options (chemotherapy, radiation, and surgery) and have found both a delay in treatment initiation and reduction in chemotherapy/hormone therapy dosage [9,14,15]. They attributed these delays or treatment reduction to possible drug-drug interactions with HAART therapy, co-infections with hepatitis, the lack of standardized treatment guidelines, and other adverse events.

While breast cancer and HIV incidence rates are independently high, the Baltimore-Washington, D.C. area has a high incidence of

both. Washington, D.C. has one of the highest incidence rates in the nation of those infected with HIV/AIDS, with approximately 2.5% of the population infected. Despite the overall number of reported cases decreasing by 39.6% between 2009 and 2013, an HIV epidemic still remains in Washington D.C., according to the World Health Organization [16]. Additionally, Baltimore City has the highest yearly infection rate of HIV in Maryland, as high as 67.5 per 100,000 [17]. Correspondingly, Washington, D.C. has one of the highest rates of breast cancer mortality. The available data from 2008 shows that breast cancer mortality in Washington, D.C. is about 27.6 per 100,000 whereas the national average is only 23.5 per 100,000 [18]. Similarly, the 2008 breast cancer mortality rate in Maryland was 25.1 per 100,000 [19]. This presents a unique opportunity for evaluation of a population with both diseases in the Baltimore-Washington, D.C. area.

The purpose of this multi-institutional demographic study is to analyze the presentation of breast cancer in a small subset of HIV-positive patients in the Baltimore-Washington D.C. area to determine if trends exist that may indicate the need for future larger scale studies.

MATERIALS AND METHODS

This study retrospectively analyzed 43 breast cancer cases in HIV-positive patients at MedStar Washington Cancer Institute (D.C.), MedStar Georgetown University Hospital (D.C.), MedStar Franklin Square Hospital Center (Baltimore), and MedStar Good Samaritan Hospital (Baltimore) from January 1, 2004 to December 31, 2014. An electronic medical record search was conducted from the hospital repository – Infomart (MedStar)– and the outpatient repository – Centricity (GE Healthcare) or Aria (Varian Medical Systems) – at each of the four MedStar hospitals in the Baltimore- Washington, DC area. Patients were identified using the diagnosis code of malignant breast cancer (ICD-9 233, 174) and the diagnosis code of HIV (ICD-9 042, V08). Inclusion criteria included patients >18 years old, female, complete electronic medical record (EMR) documentation (gender, race, age, breast cancer stage, receptor status, and surgical/adjuvant treatments). Male breast cancers were excluded from this study as no HIV-positive males were identified. The HIV status of each patient was either self-reported or retrieved from a past medical record. No HIV testing was performed upon admittance of each patient to her respective breast surgery department.

The 43 patients in the study group were compared to a 3,012-patient control group. MedStar Washington Cancer Institute's registry was chosen to identify the control group as the majority of the HIV positive patients (72.1%) were evaluated at MedStar Washington Cancer Institute. It is felt that this control cohort is a good representation of the demographics seen in the study cohort, as well as the Baltimore-Washington, D.C. area during the same 10-year period. The results were analyzed using Fisher's Exact test for categorical variables and t-tests for continuous variables, including age, race, stage at presentation, hormone receptor status, and treatment.

RESULTS

Population

A total of 43 potential HIV-positive patients with a diagnosis of breast cancer were identified from four MedStar hospitals in the Baltimore-Washington, DC area. The study population of HIV-positive breast cancer patients was compared to the population of all breast cancer patients seen at a MedStar hospital in the Baltimore-Washington, DC area. The majority of the study population was African American (90.70%). However, one Ethiopian, one Caucasian, one Asian, and one Sudanese woman were also included (Table 1). No statistical difference was found between the race of patients in the study or control group.

The date of HIV diagnosis was only available for 18 of the 43 women due to lack of EMR documentation, therefore no analysis was conducted on time or age of HIV diagnosis in relation to breast cancer diagnosis. Additionally, no information was available on the patient's HIV status, including viral loads, CD4 counts, or antiretroviral treatment regimens.

The 43 HIV-positive women were diagnosed with breast cancer between the ages of 32 and 78 years old, with an average age of 53.18 ± 9.46 years. This average age at breast cancer diagnosis was lower than the age of breast cancer diagnosis for the control population, 53.18 vs. 60.56, p=0.009 (Table 1).

Staging and Types of Breast Cancer

Patients with diagnosis of ductal carcinoma in situ (DCIS) were considered Stage 0, and those with invasive ductal carcinoma (IDC) were considered Stage I-IV based on tumor size, lymph node involvement, and metastasis. A total of 11 patients had DCIS only (25.58%) and 32 patients had IDC (74.42%). The stage of breast cancer was compared between the HIV-positive patients and the control breast cancer population (Figure 1). Median stage at diagnosis for control group was Stage I and study group was Stage II, without significant difference, p=0.31.

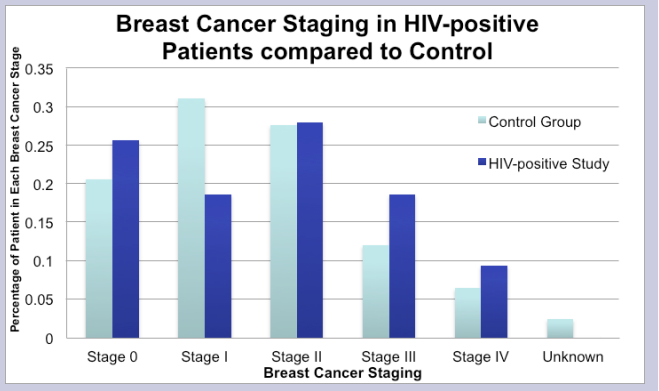

Figure 1: Breast Cancer Staging in HIV Patients Compared to Control
The percentage of patients with each breast cancer Stage 0-IV at time of diagnosis is demonstrated in this figure. Patients in the control study were in the unknown category if there was no record of the stage at diagnosis with breast cancer.

An overall general difference was found amongst hormone receptor types in the HIV population versus the control (p=0.038). When examined individually, the data shows that there is a higher percentage of luminal B (ER+/PR-/HER2-), HER2 enriched (ER-/

Table 1: A Comparison of HIV Positive Patients to All Patients in Cancer Registry with Breast Cancer Diagnosis from January 2004 to December 2014

	HIV-Positive		Control		*p*-value
Age at Breast Cancer Diagnosis					*p=0.009*
16-40	5	11.6%	180	6.0%	
41-45	3	7.0%	240	8.0%	
46-50	8	18.6%	332	11.0%	
51-55	9	20.9%	334	11.1%	
56-60	11	25.6%	446	14.8%	
61-65	4	9.3%	408	13.6%	
66-70	1	2.3%	363	12.1%	
71-75	1	2.3%	272	9.0%	
76-80	1	2.3%	200	6.6%	
80-102	0	0.0%	237	7.9%	
Race					*p = 0.12*
African American	39	90.7%	2430	80.7%	
Other	4	9.3%	582	19.3%	
Stage at Diagnosis					*p = 0.31*
0	11	25.6%	619	20.6%	
I	8	18.6%	937	31.1%	
II	12	27.9%	832	27.6%	
III	8	18.6%	360	11.9%	
IV	4	9.3%	194	6.4%	
Not available	0	0.0%	70	2.3%	
Receptor Status					*p=0.04*
Luminal A	14	32.6%	687	22.8%	*p=0.14*
Luminal B	4	9.3%	88	9.9%	*p=0.04*
Her2 Enriched	4	9.3%	55	1.8%	*p=0.009*
Basal	9	20.9%	198	6.6%	*p=0.002*
Treatment					
Surgery	38	88.4%	2697	89.5%	*p=0.80*
Radiation	30	69.8%	1869	62.1%	*p=0.34*
Chemotherapy	26	60.5%	1273	42.7%	*p=0.02*
Hormone Therapy	17	39.5%	1640	54.5%	*p=0.06*

Age, race, stage at diagnosis, receptor status, and treatment were recorded and analyzed for both the study population of HIV-positive women diagnosed with breast cancer and the control population of all women diagnosed with breast cancer at a Washington, D.C. cancer registry. Of note, luminal A is ER+/PR+/HER2-, luminal B is ER+/PR-/HER2- or ER-/PR+/HER2-, HER2-enriched is ER-/PR-/HER2+, and basal is ER-/PR-/HER2-. Ki67 was not included in the determination of Luminal A/B for this analysis.

"Other" races for the control group includes Caucasian, American Indian, Asian, Middle Eastern, Pacific Islander, and Unknown. For the study group, "other" refers to one Ethiopian, one Caucasian, one Asian, and one Sudanese woman.

PR-/HER2+), and basal types (triple negative ER-/PR-/HER2-) in our HIV-positive patients compared to the control (p=0.04, p=0.009, and p=0.002 respectively).

Treatment

Between the study and control groups, chemotherapy was the only treatment administered at a statistically significant higher rate to HIV-positive patients when compared to the control (p=0.02). Surgery, radiation, and hormone therapy did not occur at significantly different rates in the HIV-positive group as compared to the control population (Table 1).

DISCUSSION

This study evaluated the age and stage at presentation of breast cancer in HIV patients from a subset of the population in the Baltimore-Washington, D.C. area. We found that the initial age at presentation of breast cancer in the HIV cohort was lower than in the control group, 53 vs. 60 years old, p=0.009. However, the small sample size of the HIV cohort (HIV n=43, control n=3012) limits power of this study. It could be argued that the largely African American representation in the HIV-positive cohort plays a role in the early age at presentation as well as the difference in hormone receptors, as a large disparity exists amongst African American women with breast cancer compared to other ethnicities [20]. For example, African American women in general tend to have a younger age at diagnosis of breast cancer, as well as higher incidences of triple negative disease. Our study cohort was 90% African American compared to the control cohort at 80%, but controlling for race was statistically challenging due to the difference in sample size. Additionally, both the control and study groups were predominantly African-American, which is a confounding variable in our results.

Our results correspond with the data from several other retrospective studies. According to a large study of 15 databases examining patients with HIV/AIDS and cancer in the United States, no difference was found in the median age of diagnosis of breast cancer [21]. More recently, a study of 88,018 people living with HIV analyzed their age at diagnosis of non-AIDS-defining cancers. After controlling for confounding factors, they confirmed that the control population's median age at diagnosis is not statistically older than HIV-positive patients. They argue that the weighted median age was 47 [22]. When compared to these studies, the median age of breast cancer diagnosis in our HIV-positive group shows no difference. In another study of 48 HIV-positive patients with breast cancer in the Miami area from 2006-2010, the HIV cohort was more likely to be young, with a median age of 46 compared to an age of 61 in the general population [23]. When adjusting for the population at increased risk for HIV, however, this difference in age may disappear. In light of this, the difference in age at presentation warrants further investigation, especially in a largely African-American population.

We found the median stage at diagnosis for control group was Stage I and study group was Stage II, without significant difference. Our study results are consistent with the findings in Miami's HIV-positive cohort previously mentioned, in which

most HIV-positive women presented with stage II and III disease (83%), a higher rate than the general population [23]. Another retrospective review of 52 HIV-positive breast cancer patients from 1996-2011 showed that the majority of HIV patients presented with Stage 1 disease (35% vs. 22%), while non-HIV patients had more incidence of Stage III disease (21% vs. 10%) [15]. This data directly contradicts any correlation that was suspected, further indicating no difference between stage at presentation between the two groups.

A study of 1,092 women in South Africa found CD4 count to be correlated with lower age at diagnosis and Stage III/IV at presentation [24]. They attributed this correlation to aggressive chemotherapy delays in patients who had not yet begun ART and could not begin chemotherapy without ART [24]. HAART has been associated with better cancer outcomes as a result of maintaining reduced viral loads [25]. Delays in chemotherapy were also common in the study performed at the University of Maryland, suggesting that delays in treatment may be responsible for rapid progression of breast cancer [14]. Although our study did not compare CD4 counts of patients, we did observe significant differences in administration of chemotherapy between the control and study populations. The timing of treatment was not evaluated in this study, but treatment of HIV-positive patients with chemotherapy was higher than the control (60% vs. 42%, p=0.02).

In addition to HIV status, hormone receptor status of breast tumors is an important factor in treatment decisions. Our data showed higher percentage of luminal B (ER+/PR-/HER2-), HER2 enriched (ER-/PR-/HER2+), and basal types (triple negative ER-/PR-/HER2-) in HIV-positive patients compared to the control. One retrospective study similarly found HIV-positive patients to have greater numbers of triple negative tumors (19 vs. 9%) [15]. This impacted treatment, with a higher number of women receiving hormonal therapy in the non-HIV cohort. They highlighted the concept that receptor status and hormone/chemotherapy treatments cannot be discussed separately, however, as systemic treatment selection is highly weighted on the pathology and biology of the tumor. Although no conclusions can be drawn from our small sample size, further research into the topic could help decipher differences in treatment and hormone receptors in HIV-positive patients.

This study is limited in its ability to be extrapolated to all HIV-positive patients in the United States and their risk for/presentation of breast cancer. A significant limitation of this research is the lack of information regarding time of HIV diagnosis, CD4 count, and viral load. Without this information, it is difficult to make definitive conclusions about the relationship between breast cancer and HIV. This only further highlights the need for additional research. If differences in age or presentation were to hold true in a nationwide analysis, they would merit changes in screening protocols of HIV-positive women. As HIV patients live longer and treatments become more effective, the patients are now at risk for developing cancers normally seen in an aging population. Physicians should therefore aim to gain a better understanding of how to manage two diagnoses as one entity. Currently, no specific guidelines exist for treating HIV-positive breast cancer patients, despite some studies recommending earlier screening due to the aging process of HIV patients [26]. It has been suggested that as the incidence rate of breast cancer in HIV-positive patients resembles that of the general public, standard guidelines should be applied to HIV-positive patients as well [9]. Patients who are HIV-positive do not currently meet American Cancer Society's criteria for being higher than average risk [27], however, our data suggest that our subset of the population may present at an earlier age. If larger scale studies are able to expand upon these findings, there is a possibility that HIV-positive patients may benefit from earlier screening and continued annual screening throughout their lifetime.

CONCLUSION

As longevity improves in HIV-positive patients with the use of HAART, their risk for developing breast cancer continues to increase, similar to the general population. Based on the results of this retrospective study in a small cohort, HIV-positive patients may present or be treated differently than the general population. Although this study lacks generalizability due to the small sample size, the findings indicate a need for nationwide evaluation of protocols and treatments in HIV-positive women.

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DISCLOSURE

The authors have nothing to disclose.

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