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The high and heterogeneous burden of breast cancer in Hawaii: A unique multiethnic U.S. Population

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ABSTRACT

Background: While breast cancer incidence and mortality rates differ across racial/ethnic populations in the U.S., little is known about Asian and Pacific Island subpopulations. Hawaii is one of the most racially/ethnically diverse states in the U.S. Overall, Hawaii ranks 5th highest for breast cancer incidence in the nation (2010–2014) and rates have increased in recent years despite a stable national trend. In contrast, for breast cancer mortality, Hawaii has the 3rd lowest rate in the nation, with rates demonstrating a steady decline for nearly 3 decades.

Methods: We examined incidence and mortality trends from 1984–2013 across the five major racial/ethnic populations of Hawaii (Native Hawaiian, White, Japanese, Chinese, and Filipino) using Hawaii's Surveillance, Epidemiology, and End Results (SEER) registry data.

Results: With the exception of Chinese, all groups experienced increasing incidence over the thirty year period. While Japanese experienced the most pronounced recent increase, with incidence now exceeding that of Whites, their mortality rates have remained low for decades. Native Hawaiians have consistently had the highest incidence and mortality rates in the state. The incidence rates of hormone receptor (HR)-positive breast cancer were higher among Japanese and Native Hawaiians as compared to Whites. Relative to Whites, Native Hawaiians also had a higher incidence rate of the HER2-positive subtype and, Japanese, of the triple-negative (HR-/HER2-) subtype of breast cancer.

Conclusions: Studies such as this underscore the importance of considering the heterogeneity in breast cancer rates and subtypes across the different racial/ethnic populations.

1. Introduction

Breast cancer is the most common cancer in women and, despite improvements in survival, it remains the second leading cause of cancer-related death in the U.S. for women. Incidence and mortality rates vary widely across racial/ethnic populations (seer.cancer.gov). Nationally, Non-Hispanic Whites have the highest incidence, followed by African Americans, Asian/Pacific Islanders (API), American Indian/Alaska Natives (AI/AN), and Hispanics. Breast cancer mortality rates are highest in African Americans followed by non-Hispanic White, Hispanic, AI/AN, and API women with the lowest rates.

APIs are a heterogeneous group comprised of multiple Asian American and Pacific Islander subpopulations. This heterogeneity is reflected in the variation in breast cancer rates across API subpopulations. For example, incidence rates are highest among Japanese and Filipinos in the Asian API group; yet, their rates are 30% lower than that of non-Hispanic Whites [1]. In contrast, Pacific Islander API subpopulations (e.g. Native Hawaiian, Samoan, Guamanian/Chamorro) have higher incidence than each of the Asian American subpopulations. In addition, Native Hawaiians, the largest Pacific Islander subpopulation in the U.S., have higher rates than non-Hispanic Whites [2,3]. Breast cancer mortality rates also vary widely across API subpopulations with rates lower for all Asian American subpopulations, and higher for Pacific Islanders as compared to non-Hispanic Whites [4,5]. Differences in lifestyle, socioeconomic status, immigration patterns, access to care, biology, and genetics [2,6,7] likely contribute to the varied incidence and mortality rates observed for breast cancer among the API subpopulations.

Hawaii is one of the most racially/ethnically diverse states in the U.S., with no single racial/ethnic majority population. The five major

Abbreviations: APC, annual percentage change; SEER, surveillance, epidemiology, and end results; NCI, National Cancer Institute; API, Asian/Pacific Islander; AI/AN, American Indian/Alaska Native; HTR, Hawaii Tumor Registry; ER, estrogen receptor; PR, progesterone receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2

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racial/ethnic groups in Hawaii include Native Hawaiians, White, Japanese, Chinese, and the rapidly growing Filipino population. The breast cancer incidence rate for the state of Hawaii is high, ranking 5th in the U.S. for invasive breast cancer (2010–2014), with an age-adjusted incidence rate of 136 cases per 100,000 individuals compared to the national average of 124. However the mortality rate is amongst the lowest in the nation, with 15 cases per 100,000 compared to the national average of 21 (2010–2014) [8].

For this report, we utilize data from the Hawaii Tumor Registry (HTR), a founding member in 1973 of the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program, to describe breast cancer incidence, mortality, and survival for the major racial/ethnic populations in Hawaii during 1984–2013. The purpose of this evaluation is to better understand the breast cancer burden across diverse racial/ethnic subpopulations with the intent to improve prevention, screening, and treatment strategies for these groups.

2. Methods

Estimates of breast cancer incidence, mortality, and survival are calculated for the female population of Hawaii, using counts of female invasive breast cancer cases diagnosed in Hawaii (1984–2013). Hawaii state data were obtained from the HTR with clinical and pathologic data defined according to uniform national standards. (World Health Organization, International Classification of Diseases for Oncology, 3rd (ICD-O-3) ed., World Health Organization, Geneva, Switzerland, 2000; SEER Program, National Cancer Institute, SEER Program Coding and Staging Manual 2016; https://seer.cancer.gov/tools/codingmanuals/). The HTR has been a part of the NCI SEER Program since 1973.

Tumor stage was defined as localized (confined to the primary site), advanced (regional and distant; spread to regional lymph nodes or metastasized), or unknown (unstaged). Breast cancer subtype was based on the combined expression of estrogen receptor (ER) and/or progesterone receptor (PR) to define hormone receptor (HR) status, and human epidermal growth factor receptor 2 (HER2). Subtype was available for cases diagnosed in or after 2010, when collection of HER2 data became standardized across SEER registries. Cases classified as HR-positive were positive for ER and/or PR. Subtype was classified as HR + /HER2-; HR + /HER2 + ; HR-/HER2-; or HR-/HER2 + .

Average annual age-adjusted incidence and mortality rates per 100,000 were age-standardized to the 2000 U.S. Standard Population. Denominators were based on U.S. census data for the state of Hawaii, stratified by ethnicity [2]. Ninety-five percent confidence intervals were calculated for all rates. Incidence, mortality, and relative survival rates were calculated using SEER*Stat software, version 8.3.4. The Annual Percentage Change (APC) was calculated by Joinpoint regression [9]. Comparisons of cancer incidence and mortality focused on the 5 major racial/ethnic populations (White, Japanese, Native Hawaiian, Chinese, and Filipino).

3. Results

3.1. Incidence trends

Overall historical breast cancer incidence trends in Hawaii for all races were stable from 1983 to 1998, followed by a decrease from 1998 to 2006 (APC of −2.4, 95% CI −3.7 to −1.1), then increased during 2006–2014 (APC of 2.8, 95% CI 1.7 to 3.8). The APC for breast cancer incidence for the individual racial/ethnic subpopulations in Hawaii could not be calculated due to the small population sizes. Thus, we examined the trends in breast cancer incidence in 5-year periods from 1984 to 2013 for each of the 5 major ethnic groups (Fig. 1). With the exception of Chinese, the other major racial/ethnic groups demonstrated a general increase in incidence over the past thirty years, with the most pronounced increase for Japanese, from an incidence rate (per 100,000) of 93 in 1984–1988 to 154 in 2009–2013, resulting in the current incidence rate for Japanese exceeding that of Whites in Hawaii. Incidence rates for Filipinos have also increased dramatically, from 67 in 1984–1988 to 107 in 2009-2013. Native Hawaiians, who have consistently had the highest incidence rate of all the racial/ethnic populations in Hawaii, also demonstrated an increasing trend (148 to 175) over the same time period.

3.1.1. Subtype

The most common subtype observed for breast cancer cases in Hawaii (2010–2013) was HR + /HER2- (72.6%), followed by HR-/HER2- (9.2%), HR + /HER2 + (7.9%), and HR-/HER2 + (4.5%). The HR + /HER- subtype was the most common subtype for all individual racial/ethnic populations. When subtype-specific incidence rates (Table 1) were examined for the individual racial/ethnic populations compared to Whites, Native Hawaiians had a significantly higher incidence rate, compared to Whites, for three of the four breast cancer subtypes, HR + /HER2- (incidence rate ratio (IRR) 1.12, 95% CI 1.11-1.14), HR + /HER2 + (IRR 1.35, 95% CI 1.347-1.351) and HR-/HER2 + (IRR 1.19, 95% CI 1.16-1.21) and significantly lower for HR-/HER2- (IRR 0.86 95% CI 0.79-0.91). Japanese had incidence rates that were marginally higher for HR + /HER2- (IRR 1.03, 95% CI 1.03-1.04), HR + /HER2 + (IRR 1.03, 95% CI 1.02-1.05) and HR-/HER2- (IRR 1.07, 95% CI 1.07-1.09) subtypes and lower for the HR-/HER2 + (IRR 0.88, 95% CI 0.82-0.95) subtype compared to Whites. Filipinos had significantly lower incidence rates for HR + /HER2- (IRR 0.64, 95% CI 0.63-0.66), HR + /HER2 + (IRR 0.88, 95% CI 0.86-0.91), and HR-/HER2- (IRR 0.84, 95% CI 0.80-0.88). Chinese also had significantly lower incidence rates for HR + /HER2- (IRR 0.58, 95% CI 0.46-0.53), HR + /HER2 + (IRR 0.72, 95% CI 0.55-0.90), and HR-/HER2- (IRR 0.53, 95% CI 0.39-0.71) subtypes compared to Whites.

3.1.2. Stage at diagnosis

The majority of invasive breast cancers in Hawaii (2009–2013) were diagnosed at an early stage, with 65.2% diagnosed with localized breast cancer and 31.1% diagnosed with advanced (regional/distant) breast cancer (Fig. 2). Comparing the distribution of stage at diagnosis among the different racial/ethnic populations in Hawaii, Japanese women had the highest percentage of breast cancer diagnosed at the localized stage, with 72.1% diagnosed with localized breast cancer and the lowest percentage of advanced stage (26.0%). In contrast, Native Hawaiians had the lowest percentage of breast cancer diagnosed with localized stage (61.9%) and highest percentage diagnosed at the advanced stage (35.2%). When examining incidence rates by stage of diagnosis (Supplemental Table 1), Japanese had the highest incidence rates for localized stage at diagnosis compared to the other racial ethnic groups and Native Hawaiians had high incidence for both localized and advanced stage breast cancer. These trends in the distribution of stage of diagnosis across the major racial/ethnic groups have persisted for > 15 years.

3.2. Mortality trends

In Hawaii, breast cancer mortality trends were stable prior to 1986, then there was a steady decline from 1986 to 2014 (APC -1.6, 95% CI -2.1 to -1.1). The APC for breast cancer mortality trends for the individual racial/ethnic subpopulations in Hawaii could not be calculated due to the small population sizes. To illustrate the diversity in breast cancer mortality from 1984 to 2013 for the 5 major groups, we examined the trends in breast cancer mortality over three decades in 5-year time periods (Fig. 3). Whites demonstrated the greatest decreasing trend with a mortality rate (per 100,000) from 33 in 1984–1988 to 12 in 2009-2013. Native Hawaiians consistently had higher mortality rates than all other racial/ethnic groups, but similar to the other populations, demonstrated a decreasing trend in mortality from a rate of 39 in 1984–1988 to 27 in 2009-2013. The mortality rates for Japanese, Chinese, and Filipino Americans were lower than Whites and Native

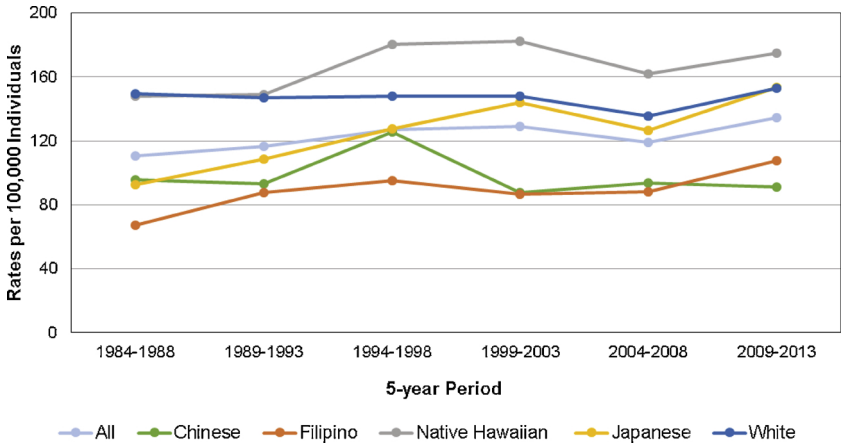

Fig. 1. Trends in age-adjusted incidence rates for invasive breast cancer among the five major racial/ethnic populations in Hawaii (1984–2013).

Hawaiians, and also demonstrated a decreasing trend. The decrease in mortality rates for these populations were less dramatic from 1984–1988 to 2009-2013: 14 to 12 for Japanese; 21 to 9 for Chinese; and 13 to 11 for Filipinos.

3.2.1. 5-year survival

We examined the 5-year survival for the different racial/ethnic populations in Hawaii. As reflected in the high mortality rates for Native Hawaiians, this population experienced poorer 5-year survival relative to the other populations (Fig. 4). This difference in survival for Native Hawaiians was most apparent in hormone receptor positive tumors (Fig. 5A), the most common breast cancer subtype. Native Hawaiians also demonstrated poorer survival for both localized and advanced stage breast cancer when compared to the other racial/ethnic groups (Fig. 5B). For Native Hawaiian breast cancer patients diagnosed with advanced stage, the survival difference was apparent as early as 3 months post diagnosis when compared with the other major racial/ethnic populations (Fig. 5B).

4. Discussion

We report on the heterogeneity in breast cancer incidence and mortality across the 5 major racial/ethnic populations (White, Japanese, Native Hawaiian, Chinese, and Filipino) of the state of Hawaii. We utilized data from the Hawaii Tumor Registry (NCI SEER Program Registry) to examine breast cancer trends for over 3 decades. In contrast to the nationwide breast cancer incidence trends, which have remained stable in recent years, breast cancer incidence has been increasing in Hawaii with an average annual increase of 2.8% (2006–2014). The high incidence rates may be the result of a high prevalence of mammographic screening for the state. Mammographic screening has been widely available in Hawaii for several decades. In the most recent report for 2016, 78% of the women ages 50–74 reported having a mammogram with the past 2 years in the U.S. and 84% for the state of Hawaii [10]. Breast cancer incidence trends for 4 of the 5 major racial/ethnic populations (all except Chinese) in Hawaii demonstrate an overall increase during 1984–2013. Hawaii Japanese had the sharpest increase, with incidence rates exceeding Whites in recent years. In addition, the incidence rates for Native Hawaiians have been consistently higher than any other population for Hawaii, including Whites. Native Hawaiian breast cancer incidence is amongst the highest in the nation. In a recent report on breast cancer trends in California, another state with a large API population [11], a significant increase in APC was reported for Asian Americans (1988–2013), along with heterogeneity in incidence rates among the different Asian American subpopulations [2–4,12,13]. However, unlike Hawaii, California incidence trends for Japanese Americans have been stable for the past 25 years [6].

Incidence for breast cancer subtypes among the racial/ethnic populations of Hawaii has not been previously reported. With the recent abstraction of HER2 by the SEER registries, molecular subtype classification was available for breast cancer cases in Hawaii for 2010-2013. When we examined the distribution of HR-positive expression in combination with HER2 expression, we found that there were differences in incidence patterns of breast cancer subtypes across racial/ethnic populations, as observed by others [6,13–15]. Japanese and Native Hawaiian women in Hawaii had higher incidence rates of HR-positive breast cancer compared to Whites, for both HR-positive tumors that were HER2-negative or positive (HR+/HER2- and HR+/HER2+). In addition, Hawaii Japanese women had a marginally higher incidence rate of the “triple negative” subtype (HR-/HER2-) compared to Whites. Interestingly, the Japanese breast cancer subtype incidence patterns in California were different from the patterns observed for Hawaii, with relative rates lower for these subtypes (HR+/HER2+; HR-/HER2-) compared to Whites [6,15]. Multiple studies have reported on Filipino women having a higher risk of the HER2-positive subtype compared to Whites in California [6,13,15,16]; however, we did not observe a significant difference in HER2-positivity for Filipino women in Hawaii.

While breast cancer mortality nationwide has been decreasing in recent years, the mortality rates for the API population have remained stable. As a state, Hawaii has the lowest breast cancer mortality in the nation and overall rates have been steadily declining for nearly three decades. Moreover, the decreasing trend in mortality was observed in each of the 5 major racial/ethnic populations. Nonetheless, while mortality rates for the individual Asian subpopulations (e.g. Japanese, Chinese, and Filipino) remain lower than Whites, Native Hawaiians continue to have the highest rates in Hawaii and second highest in the nation (after African Americans) [3].

Differences in stage at diagnosis across the racial/ethnic populations is likely the most important contributing factor for the observed heterogeneity in mortality rates. Japanese patients had the highest proportion of localized tumors at diagnosis and Native Hawaiians had the lowest in Hawaii, contributing to the notable differences in mortality. Interestingly, Filipinos had at a similar distribution for localized and advanced stage at diagnosis as Native Hawaiians, yet their mortality rates were markedly lower than Native Hawaiians. Based on the 5-year survival curves by stage of diagnosis and hormone receptor status, Native Hawaiians demonstrated the poorest survival for both localized and advanced stage at diagnosis, as well as HR positive breast cancer when compared to the other racial/ethnic populations. These results suggest that there may be some biological factors (especially for HR positive tumors) that contribute to the poorer breast cancer survival of Native Hawaiians. Recent reports comparing survival between African American and White women with ER-positive breast cancer indicate

Table 1
Incidence rates (IR) and incidence rate ratios (IRR) of invasive breast cancer of the major racial/ethnic groups in Hawaii by breast cancer subtype (Hawaii 2010–2013).

		All Ages	
	Number of Cases	IR[a] (95% CI)	IRR (95% CI)
All Subtypes			
All Races	4430	135.4 (131.3-139.5)	
White	1197	154.2 (145.0-164.0)	Ref
Japanese	1217	**158.2 (148.2-168.8)**	**1.03 (1.02-1.03)**
Native Hawaiian	817	**171.5 (159.7-183.9)**	**1.11 (1.10-1.12)**
Filipino	625	**107.0 (98.7-115.9)**	**0.69 (0.68-0.71)**
Chinese	242	**91.7 (80.0-104.8)**	**0.59 (0.55-0.64)**
Other[b]	332	**84.4 (75.3-94.3)**	**0.55 (0.52-0.58)**
HR + /HER2-			
All Races	3244	97.6 (94.2-101.1)	
White	894	114.3 (106.4-122.6)	Ref
Japanese	908	**118.1 (109.6-127.3)**	**1.03 (1.03-1.04)**
Native Hawaiian	615	**128.5 (118.4-139.3)**	**1.12 (1.11-1.14)**
Filipino	434	**73.6 (66.7-81.0)**	**0.64 (0.63-0.66)**
Chinese	176	**66.8 (56.9-78.1)**	**0.58 (0.53-0.64)**
Other	217	**56.2 (48.8-64.4)**	**0.49 (0.46-0.53)**
HR + /HER2 +			
All Races	353	11.1 (10-12.4)	
White	87	11.7 (9.1-14.7)	Ref
Japanese	84	**12.1 (9.3-15.5)**	**1.03 (1.02-1.05)**
Native Hawaiian	75	**15.7 (12.3-19.8)**	**1.35 (1.347-1.351)**
Filipino	56	**10.3 (7.8-13.4)**	**0.88 (0.86-0.91)**
Chinese	20	**8.4 (5.0-13.3)**	**0.72 (0.55-0.90)**
Other	31	**7.1 (4.8-10.1)**	**0.61 (0.53-0.69)**
HR-/HER2 +			
All Races	202	6.3 (5.5-7.3)	
White	51	6.7 (4.9-9.1)	Ref
Japanese	40	**5.9 (4.0-8.6)**	**0.88 (0.82-0.95)**
Native Hawaiian	39	**8.0 (5.7-11.0)**	**1.19 (1.16-1.21)**
Filipino	39	**6.6 (4.7-9.1)**	**0.99 (0.96-1.00)**
Chinese	18	**6.5 (3.8-10.7)**	**0.97 (0.78-1.18)**
Other	15	**3.9 (2.1-6.5)**	**0.58 (0.49-0.71)**
HR-/HER2- (Triple Negative)			
All Races	409	12.3 (11.1-13.6)	
White	106	13.3 (10.7-16.4)	Ref
Japanese	116	**14.3 (11.5-17.9)**	**1.07 (1.07-1.09)**
Native Hawaiian	54	**11.4 (8.5-15)**	**0.86 (0.79-0.91)**
Filipino	65	**11.2 (8.6-14.4)**	**0.84 (0.80-0.88)**
Chinese	19	**7.1 (4.2-11.6)**	**0.53 (0.39-0.71)**
Other	49	**12.2 (8.9-16.3)**	**0.92 (0.83-0.99)**
Unknown			
All Races	222	8.0 (7.0-9.0)	
White	59	8.3 (6.2-10.9)	Ref
Japanese	69	**7.8 (5.7-10.4)**	**0.94 (0.92-0.95)**
Native Hawaiian	34	**7.7 (5.3-10.8)**	**0.93 (0.85-0.99)**
Filipino	31	**5.3 (3.6-7.6)**	**0.64 (0.58-0.70)**
Chinese	9	**2.9 (1.2-6.0)**	**0.35 (0.19-0.55)**
Other	20	**5.0 (3.0-7.9)**	**0.60 (0.48-0.72)**

[a] Rates are age-adjusted to the U.S. Standard Population (per 100,000 individuals).
[b] Includes American Indians, Blacks, Koreans, Vietname, Micronesians, Samoans.

that African American women have a greater likelihood of dying compared to Whites [17,18]. Molecular subtyping indicated that African American women had a higher prevalence of ER-positive breast tumors that were of the PAM50-defined Luminal B subtype, a subtype associated with poor prognosis [19,20]. We have preliminary data indicating that Native Hawaiian, similar to African American women, may have also have a higher prevalence of the Luminal B subtype of ER-positive breast tumors that may be contributing to their poor survival (*unpublished;*LWML).

Our findings support the observation that there is considerable heterogeneity for both incidence and mortality in Hawaii's multiethnic population. The trends suggest that this heterogeneity has been present for multiple decades and differs from the data for API subpopulations reported for California. We also found that the molecular subtype distributions based on protein expression of hormone receptors (ER and PR) and HER2, as well as the stage at diagnosis, differ among the 5 major populations in Hawaii. We recognize that our study has limitations regarding information on lifestyle factors (e.g. obesity and dietary patterns), reproductive history, and genetics that can influence risk of breast cancer, as well as socioeconomic status, access to care, and detailed treatment information that can impact survival differences. However, despite these limitations our study provides important information regarding the differences in breast cancer profiles for the different racial/ethnic populations in Hawaii. For example, Japanese in Hawaii have experienced a sharp increase in incidence which now exceed Whites; however, this population has maintained relatively low mortality rates. Understanding the interplay of contributing factors that result in their favorable disease outcome could have critical implications to benefit other populations. Another important aspect of this study is the consistent breast cancer disparity experienced by Native Hawaiian women, who have experienced the highest incidence and mortality in the state for more than three decades. Our study highlights the importance of considering racial/ethnic heterogeneity when profiling the contributing factors for breast cancer incidence and mortality

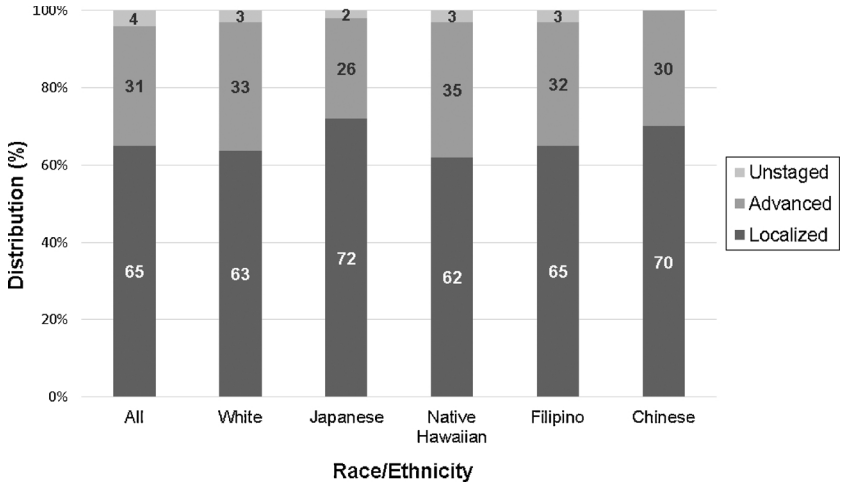

Fig. 2. Distribution of breast cancer patients by stage at diagnosis among the five major racial/ethnic populations in Hawaii (2010–2013).

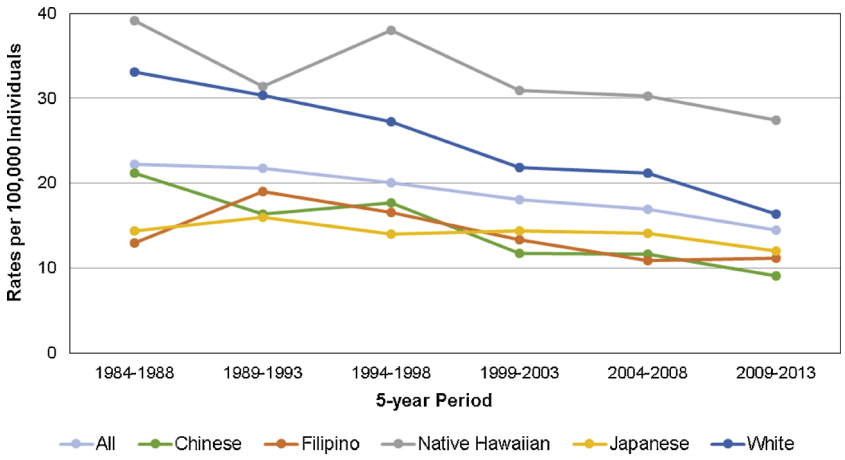

Fig. 3. Trends in age-adjusted mortality rates for invasive breast cancer among the five major racial/ethnic populations in Hawaii (1984–2013).

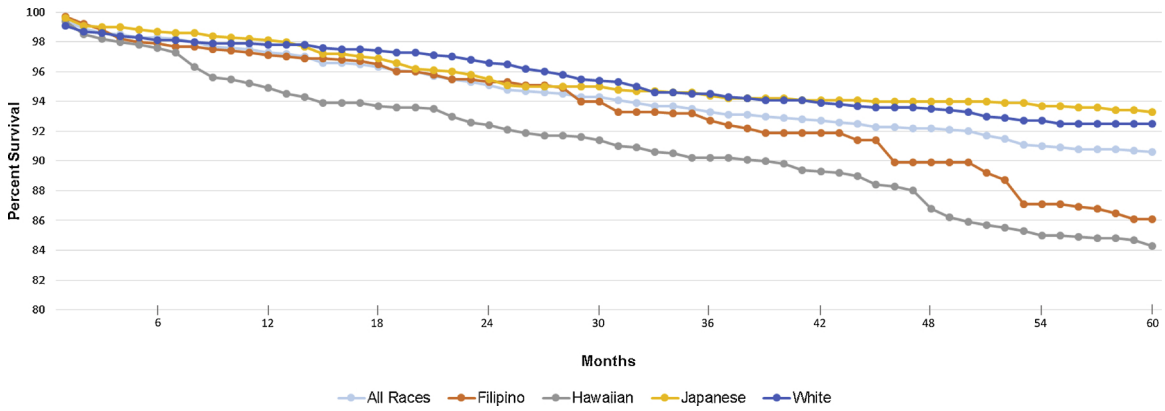

Fig. 4. Five-year relative survival for invasive breast cancer among the five major racial/ethnic populations in Hawaii (2007–2013).

in a multiethnic population.

Author contribution

Study conception and design: Lenora W.M. Loo and Brenda Y. Hernandez

Data Analysis and Interpretation: Brenda Y. Hernandez, Lenora W.M. Loo, Makana Williams

Manuscript writing: Lenora W. M. Loo and Brenda Y. Hernandez

All authors reviewed and approved of the manuscript.

Submission declaration and verification:

The work described has not been published previously and is not under consideration for publication elsewhere.

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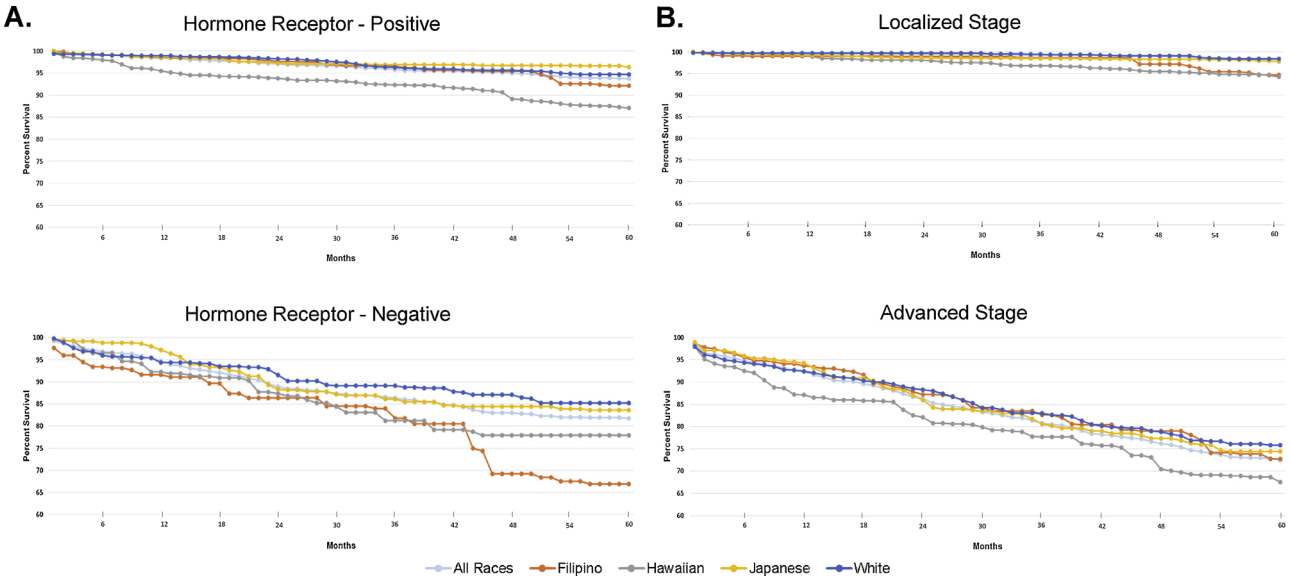

Fig. 5. Five-year survival for invasive breast cancer among the five major racial/ethnic populations in Hawaii (2007–2013) by hormone receptor status (A) and stage at diagnosis (B).

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Appendix A. Supplementary data

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