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Incident Cardiovascular Disease Risk Among Older Asian, Native Hawaiian and Pacific Islander Breast Cancer Survivors

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Abstract

Background.—Cardiotoxicity among breast cancer survivors is associated with chemotherapy and radiation therapy. The risk of cardiovascular disease (CVD) among Asian, Native Hawaiian and Pacific Islander (ANHPI) breast cancer survivors in the US is unknown.

Methods.—We used the SEER-Medicare linked database to estimate the risk of CVD among older breast cancer survivors. ICD diagnosis codes were used to identify incident CVD outcomes. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) comparing ANHPI to Non-Hispanic White (NHW) breast cancer patients for CVD, and among ANHPI race and ethnicity groups.

Results.—A total of 7,122 ANHPI breast cancer survivors and 21,365 NHW breast cancer survivors were identified. The risks of incident heart failure and ischemic heart disease were lower among ANHPI compared to NHW breast cancer survivors ($HR_{heart\ failure}$=0.72, 95%CI=0.61, 0.84; $HR_{heart\ disease}$=0.74, 95%CI=0.63, 0.88). Compared to Japanese breast cancer patients, Filipino, Asian Indian and Pakistani, and Native Hawaiian breast cancer survivors had higher risks

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of heart failure. ischemic heart disease and death. Among ANHPI breast cancer survivors, risk factors for heart failure included older age, higher comorbidity score, distant cancer stage and chemotherapy.

Conclusions.—Our results support heterogeneity in CVD outcomes among breast cancer survivors among ANHPI race and ethnicity groups. Further research is needed to elucidate the disparities experienced among ANHPI breast cancer survivors.

Impact.—Filipino, Asian Indian and Pakistani, and Native Hawaiian breast cancer patients had higher risks of heart failure, ischemic heart disease and death among ANHPI breast cancer patients.

Introduction

Approximately 58,000 cancer cases were diagnosed in the Asian, Native Hawaiian and Pacific Islander (ANHPI) population in the US in 2016.[1] Breast cancer is the most common cancer diagnosed among ANHPI women, with 11,090 cases diagnosed in 2016. The ANHPI population is incredibly heterogenous and the Asian population in the US includes individuals with origins in East Asia, Southeast Asia and the Indian subcontinent. The prevalence of cancer risk factors such as tobacco smoking, alcohol drinking and overweight/obesity are generally lower in the ANHPI population than in NHWs.[1] However, issues of concern for ANHPIs are that they are *less likely* to be diagnosed with cancer at localized stage for certain cancers compared to the NHW population, and they have *lower cancer screening* rates for cervical and colorectal cancer. They are also the only race & ethnicity group in the US that experiences cancer as the leading cause of death instead of heart disease.[2]

Cancer survivors may experience incident adverse health outcomes or late effects caused by the cancer treatment such as cardiotoxicity and cardiovascular disease (CVD).[3] Cardiotoxicity among breast cancer survivors is associated with anthracycline and HER2 inhibitor treatment, and radiation therapy.[4] There are very few large-scale cancer survivorship studies including ANHPIs, and previous studies have focused on important areas such as the impact of acculturation on quality of life,[5–7] unmet needs of Asian cancer survivors,[8,9] and survival or cause of death as outcomes.[10–13] Large scale studies of breast cancer survivors, none of which focused on ANHPI cancer survivors, have been conflicting, with some reporting increased CVD risks,[14] modestly increased CVD risks[15] or no CVD risk.[16–18] In a SEER analysis, the risks of cardiovascular mortality were lower overall for ANHPI breast cancer patients compared to NHW breast cancer patients, but for Native Hawaiian breast cancer patients, the cardiovascular mortality risk was higher than NHW breast cancer patients.[11] When comparing US-born ANHPI breast cancer patients to non-US born ANHPI breast cancer patients, increased cardiovascular mortality risks were identified in the US-born ANHPI patients.[11] There is a need to study the incidence instead of mortality due to CVD among ANHPI breast cancer survivors, and to study them by specific race and ethnicity groups among ANHPIs.

In terms of cancer treatment adherence among ANHPI breast cancer survivors, some studies reported no difference in adherence to treatment for breast cancer among ANHPI patients,

[19,20] while one study reported higher rates of adherence to chemotherapy for ANHPI breast cancer patients which was attributed to advanced cancer stage and high grade at diagnosis.[21] When comparing breast conserving surgery vs. mastectomy, ANHPI breast cancer patients were less likely to receive breast conserving surgery, regardless of education level of the patient or tumor size.[22] However, they were more likely to initiate adjuvant endocrine therapy compared to NHW women (OR=1.28, 95%CI=1.03–1.58) in a SEER-Medicare database study.[23] These treatment differences for the ANHPI population may also further contribute to disparities in late effects following breast cancer diagnosis and treatment among ANHPI cancer survivors. The aim of this study is to investigate incident CVD outcomes among older ANHPI breast cancer survivors in the SEER-Medicare data in comparison to older NHW breast cancer survivors, and to compare risks amongst specific ANHPI race and ethnicity groups.

Materials and Methods

We used the SEER-Medicare linked database from 2000 through 2020 to estimate the risk of CVD among breast cancer survivors with a population-based cohort study design. The SEER-Medicare data, consisting of two large population-based sources SEER and Medicare, contains information on demographics, cancer-related characteristics, and healthcare claims among Medicare beneficiaries with cancer. International Classification of Disease (ICD) codes are available in the Medicare claims files including claims from hospitalizations (Part A), physician/supplier bills (Part B), and institutional outpatient providers. The study was approved by the Institutional Review Board at the University of Utah and received approval for waiver of consent. Data from this study are available upon application to SEER-Medicare and IRB approval.

We included women who: 1) were age ≥66 years, 2) were diagnosed with a first primary invasive breast cancer between 2000 and 2017, 3) had continuous Medicare Parts A and B throughout the follow up period, and 4) did not have health maintenance organization (HMO) enrollment (Supplemental Figure 1). This study focused on cancer patients who were ANHPI or Non-Hispanic White (NHW). We excluded women who had less than one year of follow up or were diagnosed with cancer based on autopsy or death certificate. A breast cancer diagnosis was classified according to the SEER Site code 26000, which uses the International Classification of Diseases for Oncology, Version 3 (ICD-O-3 code: C50), excluding mesotheliomas, Kaposi's sarcoma, and lymphomas. In order to calculate baseline comorbidity scores, we started the eligibility at the age of 66 years old and required enrollment in Part A/B to be continuous a year before cancer diagnosis. Each ANHPI cancer patient was matched to up to three NHW cancer patients by exact year of diagnosis and age at the time of cancer diagnosis.

Events of CVD were identified using codes from International Classification of Disease (ICD) version 9 and 10. ICD diagnosis codes were processed with the Chronic Conditions Data Warehouse (CCW) categorizations for acute myocardial infarction, heart failure, ischemic heart disease and stroke/transient ischemic attack (Chronic Conditions Warehouse. 27 CCW Chronic Conditions Algorithms: MBSF_CC_YYYY File. REVISED 02/2022; Chronic Conditions Warehouse. 30 CCW Chronic Conditions Algorithms:

MBSF_CHRONIC_YYYY File. REVISED 02/2022). We also created a composite CVD outcome variable including all 4 of these diseases. Individuals diagnosed with the CVD diagnosis before the start of each analysis time period (1 year after cancer diagnosis) were considered as prevalent cases and were excluded for that specific outcome (Supplemental table 1). Physicians may have recorded a "rule-out" diagnosis or unconfirmed diagnoses in physician and outpatient claims. To avoid over-estimation of the outcomes, conditions ascertained by physicians and outpatient claims were required to occur more than once between 30 to 60 days.

Information on age at cancer diagnosis, year of cancer diagnosis, tumor characteristics, first-course cancer treatment (chemotherapy, hormone-based therapy, radiation, surgery), rural residence, census tract-level socioeconomic status (SES) index, and vital status was obtained from the SEER cancer file. We used the Rural-Urban Continuum codes (RUCC) to define rural counties for the county of residence at cancer diagnosis (https://www.ers.usda.gov/data-products/rural-urban-continuum-codes.aspx). The Yost index, a measure of socioeconomic status, is calculated based on a factor analysis of seven variables including average educational level, median income, poverty rate, median housing value, median rent, unemployment rate, and occupation (% working class).[24] All the breast cancer patients in our database were on Medicare but we excluded patients on supplemental insurance due to the lack of claims data on the portion of services covered by supplemental insurance. The baseline Charlson Comorbidity Index (CCI) was calculated for the one year period prior to the cancer diagnosis.[25] The ICD and CPT codes for tobacco use and obesity were also from the Chronic Conditions Data Warehouse (Chronic Conditions Warehouse. Other Chronic Health, Mental Health, and Potentially Disabling Chronic Conditions Algorithms: MBSF_OTCC_{YYYY} File. REVISED 02/2022).

Statistical analysis

Demographic and clinical characteristics between ANHPI and NHW breast cancer survivors were compared using Pearson's χ^2 tests. We also compared the demographic characteristics of ANHPI and NHW breast cancer patients, dropping the New York, Massachusetts and Idaho registries since patients from these registries did not have cancer treatment information to contribute to some of the analyses. Patients were scored as censored if they died or did not develop the CVD outcomes by the last follow-up date. We used follow-up periods with a separate model for each, to evaluate the long-term risk of CVD, >1 to 5 years and >5 years after a cancer diagnosis. Cox proportional hazards models stratified on matched pairs were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) comparing ANHPI to NHW cancer patients for each CVD outcome and for the risk of death with adjustment for potential confounders, including cancer registry, baseline CCI, residence (rural/urban), and socioeconomic status (SES). To explore differences among the ANHPI race/ethnicity groups, we chose Japanese breast cancer patients as the reference group because they were the largest ANHPI group in the data. Risk factors for heart failure were also explored for ANHPI breast cancer patients. Potential confounding factors were selected a priori based on the three properties of confounders determined by a causal model, a directed acyclic graph (DAG). Specifically, baseline CCI, rural residence, income, education and cancer registry region are risk factors for CVD (property 1), and are associated with race

and ethnicity (property 2). While cancer registry region is not a mediator (property 3), the other covariates may be on the path for the association between race and ethnicity and CVD among breast cancer patients. We were interested in the risk through alternate pathways; thus we adjusted for these factors. Baseline CCI included diagnosis of myocardial infarction, coronary heart disease, cerebrovascular accidents and transient ischemic attack before cancer diagnosis. Since we excluded prevalent events, when we estimate the risk of stroke as an example, patients who had prevalent stroke from the CCI are excluded but the model would adjust for the other previous CVD with the baseline CCI variable. The proportional hazards assumption was tested for each Cox proportional hazards model by including interactions between the predictors and time in the model. For models where the proportional hazards assumption was violated, we used flexible parametric survival models with restricted cubic splines and compared the resulting estimates to those from the Cox proportional hazards model.[26,27] Analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC).

Data availability.

The datasets used to conduct this study are available upon approval of a research protocol from the National Cancer Institute. Instructions for obtaining these data are available at https://healthcaredelivery.cancer.gov/seermedicare/obtain/

Results

A total of 7,122 ANHPI breast cancer survivors and 21,365 NHW breast cancer patients were identified in the SEER-Medicare database (Table 1). The majority of ANHPI breast cancer patients were from the Hawaii, Greater California, Los Angeles, San Francisco and New York cancer registries. In terms of the specific race/ethnicity groups, the largest proportion of ANHPI breast cancer survivors were Japanese, Chinese, and Filipino. For census-tract income level measures, ANHPI breast cancer survivors had a higher proportion in the highest income category, but a lower proportion of highest education group than NHW breast cancer patients. The highest SES category based on the Yost index had a higher proportion of ANHPI breast cancer survivors than that of NHW breast cancer survivors (31.1% vs. 26.4%), although this variable had a fairly high proportion of missing values. A baseline CCI score of 0 was less common among ANHPI breast cancer survivors (65.1% vs. 56.8%; p-value for chi-square<0.001). Obesity and tobacco use disorders were less common among ANHPI breast cancer patients compared to NHW breast cancer patients. When we compared all ANHPI and NHW breast cancer patients to the patient groups dropping the New York, Massachusetts and Idaho registries, we did not observe any differences in the demographic characteristics proportions nor with the chi-square statistics.

Demographics by specific race/ethnicity groups are shown in Supplemental Figure 2 and Supplemental table 2. The highest proportion in the highest SES groups based on the Yost index, education and income were for Asian Indian and Pakistani breast cancer patients. Lower proportions in the high SES groups were observed for Vietnamese, Native Hawaiian and other Pacific Islander breast cancer patients. Filipino and Other Pacific Islander breast cancer patients had the highest proportion of 2+ comorbidities. The proportion of breast

cancer patients with obesity and tobacco use were very low for most ANHPI groups compared to NHW breast cancer patients, with the exception of other Pacific Islander and Native Hawaiian breast cancer patients.

Compared to NHW breast cancer patients, ANHPI breast cancer patients were diagnosed with localized cancer at a slightly higher proportion, had a higher proportion of invasive ductal carcinoma, and a higher proportion of human epidermal growth factor receptor (HER2) positive tumors (Table 2). Conversely, ANHPI breast cancer patients had a lower proportion of ER/PR positive tumors than NHW breast cancer patients. ANHPI breast cancer patients underwent total mastectomies at a higher rate than partial mastectomies and had less radiation treatment compared to NHW breast cancer patients. Partial mastectomies appeared to be low in particular for Filipino, Korean and Vietnamese women (Supplemental Figure 3, Supplemental Table 3). There were no differences in chemotherapy treatment comparing ANHPI and NHW breast cancer patients.

Supplemental Figure 4 shows the incidence rates of the four CVD outcomes, ordered from higher to lower incidence. Japanese, Chinese and Korean breast cancer survivors tended to have lower incidence of most of the CVD outcomes than the other ANHPI race/ethnicity groups. The only exception was Chinese breast cancer patients who had a higher incidence of stroke than most ANHPI race/ethnicity groups at 10 per 1000 person-years. The other Pacific Islander, Asian Indian and Pakistani and Native Hawaiian breast cancer patients had the highest incidence of acute myocardial infarction and heart failure.

Compared to NHW breast cancer patients, overall ANHPI, Japanese, Chinese and other Asian breast cancer patients had a lower risk of heart failure and ischemic heart disease (Table 3). The CVD event numbers by outcome and race and ethnicity are shown in Supplemental Table 4. The proportion of ANHPI breast cancer patients diagnosed with the 4 CVD outcomes and composite CVD within 5 years of cancer diagnosis is also shown by age and race and ethnicity (supplemental table 5). However, CVD outcomes were not different between NHW breast cancer patients and Filipino, Asian Indian and Pakistani, Korean, or Vietnamese breast cancer patients. As a sensitivity analysis, we additionally adjusted for tobacco use disorders and obesity, but the inferences did not change for the CVD outcomes. We also conducted a sensitivity analysis excluding the Japanese breast cancer patients to assure that the results were not dependent on one ANHPI group (supplemental table 6); the protective HRs for heart failure and ischemic heart disease for ANHPI compared to NHW breast cancer patients were still observed.

When Japanese breast cancer patients were taken as the reference group, we observed increased risks of CVD for NHW, Filipino, Asian Indian and Pakistani and Native Hawaiian breast cancer patients >1–5 years. For specific CVDs, higher risks for heart failure and ischemic heart disease were observed for NHW and Filipino breast cancer patients in both follow up periods (Table 4). For heart failure risk >1–5 years after cancer diagnosis, increased risks were observed for Asian Indian and Pakistani, Native Hawaiian and Vietnamese breast cancer patients compared to Japanese breast cancer patients. For ischemic heart disease risk >1–5 years after cancer diagnosis, we observed increased risks for Asian Indian and Pakistani, and other Pacific Islander breast cancer patients compared

to Japanese breast cancer patients. Some of these risks persisted into the >5 year follow up period. Vietnamese breast cancer patients had an almost 8-fold increase in the risk of acute myocardial infarction compared to Japanese breast cancer patients.

Risk factors identified for heart failure among ANHPI breast cancer survivors included older age, higher CCI score, distant cancer stage, and chemotherapy treatment. Protective factors included higher income, higher SES with the Yost index, and breast cancer surgery (Table 5). Histology, HER2 status, ER status, PR status and triple negative breast cancer were not risk factors for heart failure among the ANHPI breast cancer survivors in this data. ANHPI breast cancer survivors who were diagnosed at 81–100+ years of age had a 3-fold increase in risk of heart failure compared to ANHPI breast cancer survivors diagnosed at 66–70 years of age. ANHPI breast cancer survivors diagnosed with distant cancer stage and having 2 or more comorbidities at baseline had a 2.5-fold increase in risk of heart failure.

ANHPI breast cancer patients had an overall lower risk of death compared to NHW breast cancer patients (Table 6). When separated out by ANHPI race/ethnicity groups, compared to NHW breast cancer patients, Japanese, Chinese, Other Asian, and Korean breast cancer patients had a lower risk of death. However, Native Hawaiian breast cancer patients had a higher risk of death (HR=1.33, 95%CI=1.11, 1.59) compared to NHW breast cancer patients. When Japanese breast cancer patients were taken as the reference group, Filipino, Asian Indian and Pakistani, Native Hawaiian, Vietnamese and Other Pacific Islander breast cancer patients had a higher risk of death. Heart failure diagnoses were associated with the risk of death among ANHPI breast cancer patients overall, and specifically among Japanese, Filipino, Other Asian, Asian Indian and Pakistani, and Korean breast cancer patients (Supplemental Table 7).

Discussion

While ANHPI race/ethnicity groups have been analyzed as a group in previous analyses of cancer survivorship, ANHPI are a heterogenous group in relation to CVD risk factors and SES. The risk of incident CVD diagnosis was lower among ANHPI breast cancer survivors overall, and specifically among Japanese, Chinese, and other Asian breast cancer survivors, when compared to NHW breast cancer survivors. However, comparing amongst the specific ANHPI race/ethnicity groups, we observed heterogeneity in the incidence rates of CVD. Compared to Japanese breast cancer survivors, Filipino, Asian Indian and Pakistani, and Native Hawaiian breast cancer survivors had higher risks of both heart failure and ischemic heart disease. Risk factors for heart failure included older age, higher CCI score, distant stage and chemotherapy treatment among ANHPI breast cancer survivors.

Although obesity and tobacco use disorders before cancer diagnosis were lower in prevalence among ANHPI breast cancer survivors compared to NHW breast cancer survivors, heterogeneity was observed amongst the ANHPI race and ethnicity groups. Native Hawaiian and other Pacific Islander breast cancer patients had lower proportions of patients in the highest SES group, and higher proportion of obesity and tobacco use disorders than the other ANHPI breast cancer patients. Pacific Islander breast cancer patients also had a lower proportion of local stage and higher proportions receiving chemotherapy compared to

Japanese breast cancer survivors. These risk factors may be correlated with the higher risks of heart failure and ischemic heart disease for Native Hawaiian and Pacific Islander breast cancer survivors compared to Japanese breast cancer survivors.

Filipino breast cancer survivors also had high risks of heart failure and ischemic heart disease than Japanese breast cancer survivors, along with higher proportions of 2+ comorbidities and obesity, but lower proportions of smoking. In terms of clinical factors, Filipino breast cancer patients had a lower proportion of local stage, lower proportion with partial mastectomy, and higher proportion having received chemotherapy, which may contribute to their higher risks of heart failure and ischemic heart disease.

Asian Indian and Pakistani breast cancer patients had the highest proportions in the highest education, income and SES categories. Obesity was fairly high and the proportion receiving chemotherapy was higher among Asian Indian and Pakistani breast cancer patients. Obesity and chemotherapy are risk factors for both heart failure and ischemic heart disease and may play a role in the higher risks observed among Asian Indian and Pakistani breast cancer survivors compared to Japanese breast cancer survivors. Previous studies have shown that South Asians are a higher risk of CVD, with higher genetic susceptibility to CVDs.[28, 29] Unfortunately, we did not have data on genetic susceptibility to CVD risk.

Vietnamese breast cancer survivors had lower proportions in the highest education, income and SES categories as well as lower proportions diagnosed at local stage and higher proportion receiving chemotherapy compared to both NHW and Japanese breast cancer survivors. The 2+ comorbidities was higher but obesity and smoking were lower for Vietnamese breast cancer survivors than Japanese breast cancer survivors. Higher risks of heart failure and acute myocardial infarction were observed among Vietnamese breast cancer survivors relative to Japanese breast cancer survivors. The SES difference suggest that potential differences in healthcare access may contribute to higher risks of heart failure and acute myocardial infarction.

The risk of death among ANHPI breast cancer patients were lower compared to NHW breast cancer patients, but amongst the ANHPI race and ethnicity groups, we observed heterogeneity in risks of death. The higher risk of death for Native Hawaiian breast cancer patients compared to NHW breast cancer patients may be due to higher obesity, lower SES, higher baseline comorbidities, tobacco, although we did not observe higher risks of CVD for Native Hawaiians compared to NHW breast cancer patients. The higher risk of deaths for Filipino, Asian Indian and Pakistani, Native Hawaiian, Vietnamese and Other Pacific Islander breast cancer patients compared to Japanese breast cancer patients may partly be due to incident heart failure risks.

Strengths of the study include minimal survival bias due to the longitudinal capture of the CVD outcomes in claims data. Since we do not rely on the patient to recall their disease diagnosis, the study is not subject to recall errors. This is the largest cohort study focusing on older ANHPI breast cancer patients, to our knowledge. We were able to include 1,683 Japanese, 1,404 Chinese and 1,382 Filipino breast cancer survivors who were older and on Medicare insurance. The large sample size allowed us to analyze specific ANHPI race/

ethnicity groups, which has been very limited in previous studies. We were also able to stratify on follow up time and investigate longer term adverse health outcomes among older Asian breast cancer survivors in the >5 years after cancer diagnosis time period.

Limitations of the study include the restriction to cancer patients 66 years of age and older due to the use of the SEER-Medicare data. The results are not generalizable to younger ANHPI breast cancer patients, since they may have different characteristics and generational differences in terms of smoking and obesity rates, socioeconomic status, cancer treatment distributions, as well as acculturation. The results are also not generalizable to ANHPI breast cancer patients who are on supplemental insurance plans, since we restricted to our eligibility to patients who were on Medicare only, to assure that events can be captured in the Medicare claims. Even within Medicare claims, it is possible to have missed claims or inaccurate ICD coding. However, in our previous studies, we validated identification of CVD outcomes in claims data by comparing them to self reported CVD [30–34]. Finally, we are unable to take into account factors such as physical activity, which cannot be captured even with a proxy since self-report would be needed. We added a smoking proxy variable with the tobacco use disorder and obesity as a variable with use of CPT codes. We expect that these proxy variables undercount smoking and obesity and would not capture any overweight cancer survivors. We also cannot evaluate whether there were differences in missing for smoking and obesity. However, we were able to show that obesity was a risk factor for heart failure among ANHPI breast cancer survivors. Some of the registries did not have cancer treatment information and were not included in the analysis of CVD risk factors. We compared the demographic characteristics of all cancer patients to the patient group dropping these registries and did not observe a difference. There could still be differences in cancer treatment patterns by registry that may contribute further to the CVD risk factor analysis. Finally, we do not have clinical values for risk factors such as blood pressure or cholesterol, which would have added important information to our study.

In conclusion, this is the first in-depth study of four major CVD outcomes among ANHPI breast cancer survivors with risk estimation for specific ANHPI race and ethnicity groups in the SEER Medicare data, to our knowledge. While ANHPI breast cancer survivors as a whole appear to have lower risks of CVD outcomes than NHW breast cancer survivors, the lower risks were observed only in specific ANHPI groups. Additionally, heterogeneity was observed in CVD risks, as expected, due to the heterogenous nature of ANHPI race and ethnicity groups. Our results support the expected heterogeneity in baseline and clinical characteristics, and adverse health outcomes among cancer survivors in specific ANHPI race and ethnicity groups. Our findings support that subgroups of ANHPI breast cancer survivors may face greater risks for development of CVD outcomes, which can guide targeted prevention, education, and clinical management of ANHPI breast cancer survivors. Further research is needed to elucidate the disparities experienced in CVD risks among cancer survivors in specific ANHPI race and ethnicity groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of older ANHPI and NHW breast cancer patients diagnosed 2000–2017 in the SEER Medicare data

	ANHPI (n=7,122)		NHW (n=21,365)		p-value
	n	%	n	%	
Age at cancer diagnosis [1]					1.000
66–70	2,164	30.4	6,492	30.4	
71–75	1,986	27.9	5,958	27.9	
76–80	1,498	21.0	4,494	21.0	
81–100+	1,474	20.7	4,421	20.7	
Education (census-tract level)					<0.001
20%+ non high school grads	1,740	24.4	3,359	15.7	
10 to <20% non high school grads	2,114	29.7	6,416	30.0	
5 to <10% non high school grads	1,848	25.9	6,207	29.1	
<5% non high school grads	1,385	19.4	4,963	23.2	
Unknown	35	0.5	420	2.0	
Income (census-tract level)					<0.001
<$50,000	1,881	26.4	7,061	33.0	
$50,000 to <$70,000	1,977	27.8	6,050	28.3	
$70,000 to <$90,000	1,507	21.2	3,676	17.2	
$90,000+	1,722	24.2	4,158	19.5	
Unknown	35	0.5	420	2.0	
Yost socioeconomic (SES) index (census-tract level)					<0.001
Quintile 1 (lowest SES)	364	5.1	1,752	8.2	
Quintile 2	613	8.6	2,586	12.1	
Quintile 3	818	11.5	3,189	14.9	
Quintile 4	1,420	19.9	4,007	18.8	
Quintile 5 (highest SES)	2,217	31.1	5,639	26.4	
Unknown	113	1.6	297	1.4	
Missing	1,577	22.1	3,895	18.2	
RUCC					<0.001
Urban	6,747	94.7	17,952	84.0	
Rural	373	5.2	3,411	16.0	
Modified Baseline CCI [2]					<0.001
0	4,045	56.8	13,919	65.1	
1	1,957	27.5	4,794	22.4	
2+	1,120	15.7	2,652	12.4	
Obesity before cancer diagnosis					<0.001
No	6,644	93.3	18,620	87.2	
Yes	478	6.7	2,745	12.8	
Tobacco use disorder before cancer diagnosis					<0.001

	ANHPI (n=7,122)		NHW (n=21,365)		p-value
	n	%	n	%	
No	7,004	98.3	20,195	94.5	
Yes	118	1.7	1,170	5.5	
Race/ethnicity [3]					<0.001
Japanese	1,683	23.6			
Chinese	1,404	19.7			
Filipino	1,382	19.4			
Other Asian	875	12.3			
Asian Indian and Pakistani	533	7.5			
Korean	398	5.6			
Native Hawaiian	370	5.2			
Vietnamese	312	4.4			
Other Pacific Islander	165	2.3			

ANHPI, Asian, Native Hawaiian and Pacific Islander; NHW, Non-Hispanic White; RUCC, Rural-Urban Commuting Area Codes,

[1] NHW breast cancer patients were matched to ANHPI breast cancer patients on age and year of diagnosis,

[2] Charlson comorbidity Index was modified to exclude CVDs,

[3] 1.4% (n=98) of ANHPI were Hispanic

Table 2.

Clinical characteristics of older breast cancer survivors, diagnosed from 2000 to 2017, SEER-Medicare

	ANHPI (n=7,122)		NHW (n=21,365)		p-value
	n	%	n	%	
Cancer stage					<0.001
Localized	5,050	70.9	15,027	70.3	
Regional	1,703	23.9	4,995	23.4	
Distant	226	3.2	731	3.4	
Unknown	143	2.0	612	2.9	
Histology					<0.001
Ductal carcinoma	5,289	74.3	14,644	68.5	
Lobular	1,112	15.6	4,886	22.9	
Mucinous or colloid	296	4.2	613	2.9	
Medullary	11	0.2	38	0.2	
Other histology type	414	5.8	1,184	5.5	
HER2[a, b]					0.011
Positive	423	12.3	875	10.3	
Negative	2,793	81.3	7,038	82.8	
Borderline	76	2.2	186	2.2	
Unknown	144	4.2	399	4.7	
ER status [b]					<0.001
ER+	5,041	80.0	12,539	81.7	
ER−	871	13.8	1,782	11.6	
Borderline	**		15	0.1	
Unknown	**		1,020	6.6	
PR status [b]					0.037
PR+	4,327	68.7	10,687	69.6	
PR−	1,549	24.6	3,536	23.0	
Borderline	29	0.5	67	0.4	
Unknown	393	6.2	1,066	6.9	
Received surgery [b]					<0.001
None; no surgery of primary site; autopsy only	429	6.8	1,078	7.0	
Partial mastectomy	3,309	52.5	9,224	60.1	
Total (simple) mastectomy	1,227	19.5	2,288	14.9	
Modified radical mastectomy	1,261	20.0	2,561	16.7	
Other	54	0.9	144	0.9	
Unknown	18	0.3	61	0.4	
Received radiotherapy [b]					<0.001
None	3,213	51.0	7,422	48.3	
External Beam	2,776	44.1	6,917	45.0	
Other[c]	156	2.5	556	3.6	

	ANHPI (n=7,122)		NHW (n=21,365)		p-value
	n	%	n	%	
Unknown	153	2.4	461	3.0	
Received chemotherapy [b]					0.215
No/unknown	4,999	79.4	12,303	80.1	
Yes	1,299	20.6	3,053	19.9	

Abbreviation: ER, estrogen receptors; PR, progesterone receptors; HR, hormone receptor; HER2, human epidermal growth factor receptor 2

[a] Available for the breast cancer patients diagnosed from 2010 to 2017

[b] Excluded patients from Idaho, New York, Massachusetts registries due to missing treatment and HER2 information

[c] Radioactive implants, radioisotopes, combination of beam radiation with radioactive implants or radioisotopes, radiation with method or source not specified

** cell sizes <11 have been suppressed. An additional cell may be suppressed so that the cell size <11 cannot be derived from subtraction

Table 3.

The risks of incident cardiovascular diseases (HRs[a] and 95%CIs) among older ANHPI and NHW breast cancer survivors in SEER-Medicare, stratified by follow-up period

	NHW	Asian, Native Hawaiian and Pacific Islander	Japanese	Chinese	Filipino	Other Asian
>1–5 years						
Composite CVD	Reference	0.83 (0.72, 0.95)	0.64 (0.49, 0.84)	0.78 (0.61, 1.01)	1.05 (0.82, 1.34)	0.63 (0.47, 0.84)
Acute Myocardial Infarction	Reference	0.85 (0.59, 1.22)	0.60 (0.25, 1.44)	0.46 (0.22, 0.97)	1.23 (0.66, 2.31)	0.64 (0.29, 1.40)
Heart Failure	Reference	0.72 (0.61, 0.84)	0.45 (0.32, 0.62)	0.57 (0.43, 0.77)	0.97 (0.74, 1.27)	0.56 (0.39, 0.79)
Ischemic Heart Disease	Reference	0.74 (0.63, 0.88)	0.49 (0.35, 0.68)	0.69 (0.52, 0.93)	0.93 (0.69, 1.24)	0.67 (0.46, 0.96)
Stroke	Reference	0.84 (0.69, 1.02)	0.74 (0.50, 1.08)	0.88 (0.63, 1.23)	1.00 (0.70, 1.44)	0.70 (0.46, 1.06)
>5 years						
Composite CVD	Reference	0.65 (0.55, 0.76)	0.57 (0.42, 0.76)	0.60 (0.44, 0.81)	0.82 (0.60, 1.13)	0.56 (0.39, 0.80)
Acute Myocardial Infarction	Reference	0.64 (0.46, 0.90)	0.65 (0.36, 1.15)	0.42 (0.20, 0.87)	0.68 (0.39, 1.20)	0.84 (0.39, 1.78)
Heart Failure	Reference	0.74 (0.63, 0.87)	0.54 (0.40, 0.72)	0.66 (0.50, 0.89)	1.04 (0.78, 1.39)	0.69 (0.48, 0.98)
Ischemic Heart Disease	Reference	0.58 (0.47, 0.70)	0.47 (0.33, 0.67)	0.47 (0.33, 0.67)	0.79 (0.54, 1.14)	0.46 (0.30, 0.71)
Stroke	Reference	0.73 (0.59, 0.91)	0.71 (0.49, 1.02)	0.65 (0.44, 0.96)	0.91 (0.61, 1.34)	0.69 (0.43, 1.11)

	Asian Indian and Pakistani	Korean	Native Hawaiian	Vietnamese	Other Pacific Islander
>1–5 years					
Composite CVD	1.31 (0.90, 1.91)	0.70 (0.44, 1.09)	1.19 (0.74, 1.92)	0.93 (0.59, 1.45)	0.91 (0.48, 1.74)
Acute Myocardial Infarction	1.20 (0.56, 2.61)	0.22 (0.03, 1.91)	1.00 (0.24, 4.20)	4.41 (0.86, 22.57)	2.17 (0.54, 8.75)
Heart Failure	1.07 (0.72, 1.58)	0.72 (0.42, 1.21)	1.15 (0.68, 1.93)	1.11 (0.65, 1.90)	0.82 (0.42, 1.61)
Ischemic Heart Disease	1.11 (0.71, 1.76)	0.64 (0.38, 1.09)	0.73 (0.40, 1.33)	0.75 (0.43, 1.28)	1.15 (0.55, 2.42)
Stroke	1.20 (0.70, 2.06)	0.54 (0.27, 1.08)	0.92 (0.48, 1.77)	0.93 (0.42, 2.07)	0.74 (0.28, 1.95)
>5 years					
Composite CVD	0.73 (0.44, 1.20)	0.69 (0.30, 1.19)	1.14 (0.64, 2.03)	0.79 (0.44, 1.45)	0.60 (0.27, 1.35)
Acute Myocardial Infarction	0.30 (0.08, 1.09)	0.96 (0.40, 2.28)	0.19 (0.05, 0.66)	0.82 (0.30, 2.26)	0.37 (0.04, 3.63)
Heart Failure	0.80 (0.45, 1.41)	1.04 (0.60, 1.79)	1.59 (0.90, 2.79)	0.79 (0.44, 1.43)	0.67 (0.24, 1.85)
Ischemic Heart Disease	0.91 (0.49, 1.69)	0.63 (0.33, 1.19)	1.02 (0.53, 1.99)	0.73 (0.35, 1.52)	1.17 (0.42, 3.31)
Stroke	1.15 (0.64, 2.07)	0.50 (0.22, 1.13)	0.74 (0.35, 1.57)	0.74 (0.36, 1.50)	0.12 (0.02, 0.92)

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Abbreviation: HR, hazard ratio; CI, confidence interval

[a]Models adjusted for baseline Charlson Comorbidity Index, cancer registry, rural residence, census tract income, census tract education

Table 4.

The risks of incident cardiovascular disease (HRs[a] and 95%CIs) among older ANHPI and NHW breast cancer survivors in SEER-Medicare, stratified by follow-up period

	NHW	Japanese	Chinese	Filipino	Other Asian
>1–5 years					
Composite CVD	1.57 (1.20, 2.05)	Reference	1.23 (0.88, 1.72)	1.64 (1.19, 2.27)	0.99 (0.67, 1.45)
Acute Myocardial Infarction	1.58 (0.66, 3.78)	Reference	0.65 (0.22, 1.89)	2.91 (0.76, 5.28)	1.06 (0.34, 3.29)
Heart Failure	2.22 (1.61, 3.08)	Reference	1.34 (0.89, 2.02)	2.26 (1.55, 3.32)	1.31 (0.81, 2.10)
Ischemic Heart Disease	1.96 (1.40, 2.75)	Reference	1.41 (0.94, 2.13)	1.83 (1.22, 2.73)	1.31 (0.81, 2.13)
Stroke/Transient Ischemic Attack	1.36 (0.92, 2.01)	Reference	1.22 (0.77, 1.95)	1.42 (0.88, 2.27)	0.99 (0.57, 1.71)
>5 years					
Composite CVD	1.77 (1.32, 2.37)	Reference	1.06 (0.73, 1.54)	1.46 (1.00, 2.12)	0.99 (0.63, 1.54)
Acute Myocardial Infarction	1.47 (0.82, 2.62)	Reference	0.58 (0.25, 1.32)	1.04 (0.24, 1.32)	1.17 (0.47, 2.94)
Heart Failure	1.89 (1.42, 2.51)	Reference	1.27 (0.88, 1.84)	1.92 (1.34, 2.75)	1.34 (0.86, 2.08)
Ischemic Heart Disease	2.30 (1.62, 3.26)	Reference	1.08 (0.69, 1.69)	1.82 (1.16, 2.84)	1.06 (0.62, 1.81)
Stroke/Transient Ischemic Attack	1.37 (0.95, 1.97)	Reference	0.92 (0.57, 1.49)	1.27 (0.79, 2.04)	0.96 (0.54, 1.69)

	Asian Indian and Pakistani	Korean	Native Hawaiian	Vietnamese	Other Pacific Islander
>1–5 years					
Composite CVD	2.05 (1.30, 3.24)	1.09 (0.66, 1.80)	1.86 (1.15, 3.01)	1.45 (0.87, 2.42)	1.43 (0.73, 2.82)
Acute Myocardial Infarction	2.01 (0.63, 6.41)	0.31 (0.31, 3.08)	1.66 (0.41, 6.82)	7.92 (1.27, 49.4)	3.60 (0.75, 17.23)
Heart Failure	2.46 (1.48, 4.09)	1.58 (0.88, 2.85)	2.65 (1.56, 4.52)	2.50 (1.34, 4.64)	1.88 (0.91, 3.87)
Ischemic Heart Disease	2.18 (1.24, 3.82)	1.28 (0.80, 2.34)	1.63 (0.88, 2.99)	1.57 (0.85, 2.90)	2.30 (1.04, 5.07)
Stroke/Transient Ischemic Attack	1.77 (0.91, 3.42)	0.74 (0.34, 1.62)	1.24 (0.65, 2.37)	1.24 (0.52, 3.00)	1.05 (0.38, 2.90)
>5 years					
Composite CVD	1.28 (0.72, 2.28)	1.23 (0.68, 2.21)	2.02 (1.18, 3.48)	1.41 (0.73, 2.69)	1.06 (0.46, 2.46)
Acute Myocardial Infarction	0.41 (0.10, 1.61)	1.36 (0.52, 3.57)	0.30 (0.09, 1.02)	1.17 (0.38, 3.60)	0.59 (0.06, 5.90)
Heart Failure	1.59 (0.85, 2.96)	2.01 (1.12, 3.60)	2.97 (1.71, 5.15)	2.51 (0.79, 2.86)	1.26 (0.44, 3.55)
Ischemic Heart Disease	2.05 (1.01, 4.12)	1.45 (0.72, 2.93)	2.35 (1.25, 4.45)	1.60 (0.73, 3.52)	2.58 (0.88, 7.55)
Stroke/Transient Ischemic Attack	1.59 (0.81, 3.12)	0.69 (0.29, 1.63)	1.01 (0.50. 2.05)	1.00 (0.46, 2.18)	0.19 (0.03, 1.52)

Abbreviation: HR, hazard ratio; CI, confidence interval

[a]Models adjusted for baseline Charlson Comorbidity Index, cancer registry, rural residence, census tract income, census tract education

Table 5.

Risk factors for heart failure among ANHPI breast cancer survivors in SEER Medicare

	no heart failure (n)	heart failure (n)	HR	95%CI	p for trend
Age of cancer diagnosis [1]					
66–70	1,853	223	1.00		
71–75	1,571	262	1.38	(1.15, 1.64)	
76–80	1,105	246	2.03	(1.69, 2.44)	<0.001
81–100	988	240	3.05	(2.52, 3.68)	
Education (census-tract level) [2]					
20%+ non high school grads	1,265	284	1.00		
10 to <20% non high school grads	1,611	206	0.86	(0.72, 1.03)	
5 to <10% non high school grads	1,466	230	0.97	(0.78, 1.20)	0.685
<5% non high school grads	1,149	148	0.93	(0.70, 1.22)	
Income (census-tract level) [3]					
<$50,000	1,373	308	1.00		
$50,000 to <$70,000	1,494	311	0.98	(0.83, 1.17)	
$70,000 to <$90,000	1,197	187	0.85	(0.68, 1.05)	0.005
$90,000+	1,426	162	0.66	(0.50, 0.87)	
Yost socioeconomic index (census-tract level) [4]					
Quintile 1 (lowest SES)	270	55	1.00		
Quintile 2	467	64	0.63	(0.44, 0.90)	
Quintile 3	629	121	0.95	(0.69, 1.32)	0.004
Quintile 4	1,141	149	0.68	(0.50, 0.93)	
Quintile 5 (highest SES)	1,833	215	0.61	(0.45, 0.84)	
Baseline Charlson comorbidity Index [5]					
0	3,180	445	1.00		
1	1,519	292	1.39	(1.19, 1.62)	<0.001
2+	792	231	2.56	(2.17, 3.02)	
Obesity [6]					
No	5,107	889	1.00		
Yes	290	61	1.37	(1.04, 1.80)	
Cancer stage [6]					
Localize	3955	668	1.00		
Regional	1273	249	1.28	(1.10, 1.49)	
Distant	169	202	2.59	(1.82, 3.69)	<0.001
Surgery [7]					
None	253	42	1.00		
Local tumor destruction, NOS	2628	439	0.62	(0.44, 0.87)	
Subcutaneous mastectomy	965	**	0.70	(0.48, 1.01)	
Total (simple) mastectomy	917	208	0.57	(0.40, 0.81)	

	no heart failure (n)	heart failure (n)	HR	95%CI	p for trend
Other	38	**	1.33	(0.62, 2.87)	
Radiotherapy [8]					
None	2341	446	1.00		
External Beam	2220	375	0.88	(0.76, 1.01)	
Other	135	11	0.59	(0.32, 1.07)	
Chemotherapy [9]					
No	3801	656	1.00		
Yes	1006	192	1.37	(1.15, 1.64)	

Potential risk factors investigated with no association: insurance status, tobacco use disorders, rural residence, histology, HER2, ER, PR

1. adjusted on race, SEER registry region, CCI

2. adjusted on race, SEER registry region, age, income, RUCC,

3. adjusted on race, SEER registry region, age, education, RUCC,

4. adjusted on race, SEER registry region, age, RUCC

5. adjusted on race, SEER registry region, age, income, education, RUCC

6. adjusted on race, SEER registry region, age, income, education, RUCC, CCI, cancer treatment

7. adjusted on race, SEER registry region, age, income, education, RUCC, CCI, stage

8. adjusted on race, SEER registry region, age, income, education, RUCC, CCI

9. adjusted on race, SEER registry region, age, income, education, RUCC, CCI

** cell sizes <11 have been suppressed. An additional cell may be suppressed so that the cell size <11 cannot be derived from subtraction

Table 6.

Risk of death among breast cancer survivors

	Died		Alive		HR (95% CI) for risk of death
	N	%	N	%	
Race/ethnicity					
NHW	5,618	72.2	7,995	66.8	Reference
ANHPI	2,165	27.8	3,976	33.2	0.78 (0.71, 0.85)
Race/ethnicity					
NHW	5,618	72.2	7,995	66.8	Reference
Japanese	609	7.8	982	8.2	0.65 (0.56, 0.75)
Chinese	413	5.3	677	5.7	0.73 (0.63, 0.85)
Filipino	449	5.8	801	6.7	1.01 (0.87, 1.18)
Other Asian	181	2.3	544	4.5	0.64 (0.52, 0.79)
Asian Indian and Pakistani	101	1.3	279	2.3	0.79 (0.60, 1.04)
Korean	95	1.2	240	2.0	0.75 (0.56, 0.99)
Native Hawaiian	169	2.2	184	1.5	1.33 (1.11, 1.59) *
Vietnamese	95	1.2	175	1.5	0.94 (0.70, 1.27)
Other Pacific Islander	53	0.7	94	0.8	0.86 (0.57, 1.31)
Race/ethnicity (ANHPI only) **					
Japanese	626	28.0	1,006	24.7	Reference
Chinese	425	19.0	695	17.1	1.12 (0.98, 1.28)
Filipino	465	20.8	818	20.1	1.50 (1.32, 1.70)
Other Asian	187	8.4	556	13.7	1.09 (0.91, 1.30)
Asian Indian and Pakistani	102	4.6	285	7.0	1.27 (1.02, 1.60)
Korean	101	4.5	242	6.0	1.12 (0.90, 1.39)
Native Hawaiian	172	7.7	189	4.6	2.14 (1.79, 2.55)
Vietnamese	98	4.4	178	4.4	1.47 (1.17, 1.84)
Other Pacific Islander	56	2.5	97	2.4	1.71 (1.29, 2.26)

* Flexible model

** different counts from model above since we included patients without a NHW patient match

Abbreviation: ANHPI, Asian, Native Hawaiian and Pacific Islander; NHW, Non-Hispanic White

All models adjusted for baseline Charlson Comorbidity Index, cancer stage, cancer registry, rural residence, socioeconomic status, cancer diagnosis age, cancer diagnosis year.

Patients from Idaho, New York, Massachusetts registries were excluded due to missing death information.