

Research Article

Breast Cancer in Native American Women: A Population Based Outcomes Study involving 863,958 Patients from the Surveillance Epidemiology and End Result (SEER) Database (1973-2010)

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Received: 01 December 2017; **Accepted:** 11 December 2017; **Published:** 18 December 2017

Citation: Shilpa Gopinath, Gopinath KV. Breast Cancer in Native American Women: A Population Based Outcomes Study involving 863,958 Patients from the Surveillance Epidemiology and End Result (SEER) Database (1973-2010). Journal of Cancer Science and Clinical Therapeutics 1 (2017): 22-31.

Abstract

Background: Breast cancer is the most common cancer among Native American (NA) women. Despite this fact, existing data suggests NA women have a lower-than-expected breast cancer incidence rates, but a markedly higher mortality to incidence ratio compared to other racial/ethnic groups. This study sought to analyze demographic and clinical factors in a large NA breast cancer cohort to validate these observations and to delineate clinical and pathological factors which may better risk stratify this unique population for optimal treatment protocols and clinical trial accrual.

Methods: Demographic and clinical data on 863,958 women with carcinoma of the breast was extracted from the Surveillance Epidemiology and End Result (SEER) database (1973-2010). Standard statistical methodology was used.

Results: Among 863,958 breast cancer patients, 4,289 (0.5%) were NAs and 859,669 (99.5%) were non-Hispanic white (NHW) women. The majority of breast cancer in both groups occurred among those aged 60 to 79 years (33.5% NA vs. 43.7% NHW). NA women had a higher incidence of breast cancer at a younger age (9.2% NA vs. 5.1% NHW for age 20-39, and 51.8% NA vs. 38.1% NHW at age 40-59; $p < 0.001$), and a higher rate of regional (34.0% NA vs. 31.2% NHW) and distant metastasis (7.9% NA vs. 6.1% NHW). The majority of women in both groups had tumor size < 2 cm (56.4%) and moderately differentiated tumor (42.3%; $p < 0.001$). Mean overall survival (OS) was significantly

longer in NHW women than NAs (7.40±6.7 vs. 6.66±6.1 years; $p<0.001$). The majority (54.3%) of all patients underwent surgery only. Cancer specific mortality (21.7%NA vs. 21.2%NHW) and 1-year cumulative survival (94%) was similar between the two groups. The 5-year survival rate was lower in NA women (74%NA vs. 76% NHW). Multivariate analysis identified that age>60 (OR 1.3), size >4cm (OR 1.8) and distant metastasis (OR 3) were associated with increased mortality; $p<0.001$.

Conclusions: Breast cancer affects the NA population far less often than NHW women. NA breast cancer patients tend to be younger and present with more aggressive disease features and have lower survival rates compared to women in other ethnic groups. Surgical resection and combination surgery and radiation treatment confers the greatest survival advantage in NA women compared to NHW. In light of these disparities, and to better understand the breast cancer burden and associated risk factors, NA women should be considered for clinical trial accrual to delineate genetic and environmental factors which influence incidence rates and prognosis.

Introduction

Breast cancer is the second leading cause of cancer death among women in the United States (US) and the most common cancer diagnosed, accounting for nearly one in three cancers [1-4]. Approximately 231,840 new cases of invasive breast cancer, 60,290 new diagnoses of ductal carcinoma *in situ* (DCIS) and 40,290 deaths were expected among women of all races/ethnicities in the year 2015 [5]. Female breast cancer incidence rates have been declining since the year 2000, and decreased further by 7% from 2002 to 2003 after reports of the association of hormone therapy with breast cancer was published by the Women's Health Initiative [6].

The incidence of breast cancer is 91.9/100,000 NA women compared to 128.1/100,000 NHW women and the lifetime risk (up to age 85) of breast cancer is 8% for NA women and 13% for NHW women [7]. Breast cancer incidence and mortality rates vary according to where NA women live [8]. NA women living in Alaska have the highest incidence rates while women who live in the Southwest have the lowest incidence rates [8]. The mean age of diagnosis is 53.5 years for NA women compared to 63.4 years for NHW women [9]. Breast cancer is also the third leading cause of mortality among NA women and 26% of NA women die from it [10]. The mortality rate is 15/100,000 NA women versus 21.9/100,000 NHW women [7]. Like incidence, NA women who live in Alaska and the Southern Plains have the highest mortality rate and those who live in the Southwest have the lowest mortality rate [11]. Although breast cancer incidence and mortality rates declined significantly each year among women in the US, and NHW women in particular, incidence and mortality rates remains unchanged for NA women [8,5].

Current knowledge regarding breast cancer among NA women is limited and determining the breast cancer burden among NA women has been difficult largely due to underreporting among this racial/ethnic minority group, lack of data collection in many areas of the country and classification of NAs as a whole among other minority groups. The current study examines a large cohort of NA breast cancer patients from the Surveillance, Epidemiology and End Results database in an effort to more precisely identify demographic, clinical and treatment strategies that impact clinical outcomes.

Methods

Demographic and clinical data for the current study was extracted from the Surveillance, Epidemiology, and End

Results (SEER) database provided by the National Cancer Institute between 1973 and 2010. SEER Stat version 8.0.4 was utilized to extract data from 18 SEER registries (Alaska Native Tumor Registry, Arizona Indians, Cherokee Nation, Connecticut, Detroit, Georgia Center for Cancer Statistics, Greater Bay Area Cancer Registry, Greater California, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Jersey, New Mexico, Seattle-Puget Sound, and Utah). A total of 863,958 patients with histologically confirmed breast cancer were identified and exported to IBM SPSS® v23.0 (IBM Corporation, Armonk, NY, USA). Patients with a primary diagnosis of breast cancer were identified to form the final study cohort, using the SEER International Classification of Disease for Oncology (ICD-O-3) code C174.0-C174.9. The breast cancer patients were further subdivided into NA & NHW women. Demographic and clinical data extracted included age, stage, tumor size, grade, lymph node and type of treatment received (surgery, radiation, both or unknown/no treatment). The term “no treatment” refers to no reported treatment. Patients with in situ cancers and those in whom histologic confirmation of their cancer was not available were excluded from the final study cohort. Endpoints examined included overall survival, mortality, and cancer-specific mortality. Categorical variables were compared using the *Chi* square test, and continuous variables were compared using Student’s t test and analysis of variance (ANOVA). Multivariate analysis using the ‘Backward Wald’ method was performed to identify factors that influenced mortality. Missing and unknown data was excluded from the multivariate analysis. Statistical significance was accepted at the level of $p < 0.05$.

Results

Demographic data

A total of 863,958 breast cancer cases were reported in the SEER database over the 38-year study period (1973-2010). Among 863,958 breast cancer patients, 4,289 (0.5%) were NA’s and 859,669 (99.5%) were NHW’s. The breast cancer incidence was lowest in the under 20 age group. In the 20-to-39-year age group, the incidence of breast cancer was 9.2% in NA’s and 5.1% in NHW’s and in the 40-to-59-year age group, there were 51.8% NA women and 38.1% NHW women diagnosed with breast cancer. The majority of breast cancer cases in both groups occurred in the age group 60 to 79 years (33.5% NA vs. 43.7% NHW; $p < 0.001$), while in women above 80 years NA women had a lower incidence of breast cancer (5.5% NA vs. 13.1% NHW; $p < 0.001$).

Tumor characteristics

NA women had a lower rate of localized disease (58.1% NA vs. 62.5% NHW) and a higher rate of regional (34.0% NA vs. 31.3% NHW) and distant metastasis (7.9% NA vs. 6.1% NHW). The majority of women in both groups had tumor size < 2 cm (56.4%) with fewer NA than NHW women. (50.9% NAs vs. 56.5% NHW). NAs presented with larger tumor size with 35.2% having a tumor size between 2cm. to 4cm. compared to 32.9% in NHW women and 13.4% with tumor size more than 4cm. compared to 10.4% NHW women. NHW’s had more well differentiated tumors compared to NA women (18.2% NA vs. 20.6% NHW) Women in both groups had a higher percentage of moderately differentiated (42.3% overall; 38.9% NA vs. 42.3% NHW, $p < 0.001$) & poorly differentiated tumors (34.7% overall, 40.4% NA vs. 34.6% NHW, $p < 0.001$). Undifferentiated tumor grade was equal in both groups (2.5%). NA women presented with more lymph node positive disease compared to NHW women (38.3% NA vs. 32.9% NHW).

Treatment and clinical outcomes

Overall, 4.9% did not undergo any treatment (5.6% NA vs 4.9% NHW; $p < 0.01$) and 1.2% of women in both groups (1.3% NA vs. 1.2% NHW; $p < 0.01$) underwent only radiation therapy. A majority (54.3%) of all patients underwent surgery only and 39.7% underwent surgery and radiation. Fewer NAs underwent primary surgical resection alone (52.5% NA vs. 54.3% NHW; $p < 0.01$) with a slightly higher percent undergoing a combination of surgery and radiation therapy (40.6% NA vs. 39.6% NHW; $p < 0.01$). Overall mortality was lower in NA women (35.3%) compared to NHW women (39.9%); $p < 0.01$. Cancer specific mortality (21.7% NA vs. 21.2% in NHW; $p < 0.01$) as well as 1-year cumulative survival (94%; $p < 0.01$) was similar between both groups. Mean overall survival (OS) was significantly lower in NA women than NHWs (6.66±6.05 years in NA vs 7.40±6.69 in NHW; $p < 0.001$). NA women had a lower 5-year survival compared to NHW (74% NA vs. 76% NHW; $p < 0.01$).

Multivariable analysis

Multivariate analysis identified, age >60 years (OR 1.3), size >4cm (OR 1.8) and distant metastasis (OR 3) as independently associated with increased mortality, $p < 0.001$.

Discussion

Racial disparities in breast cancer

Breast cancer incidence and mortality rates in women vary across ethnic and racial groups. Lower breast cancer incidence rates in NA women are attributed to the variation in the prevalence of risk factors compared to women of other ethnicities [12]. NA women have a greater number of children, and have their first child at younger ages, both of which are protective against breast cancer [13]. Also they are more likely to breastfeed for at least a year and have lower rates of alcohol consumption and obesity, which are generally associated with lower breast cancer risk [14-16].

Family history and genetics have also been known to influence incidence of breast cancer among NA women. Slattery *et al.* explored the biological basis of disparities in breast cancer risk by evaluating genetic variation in 16 IL genes involved in inflammation, insulin and energy homeostasis in conjunction with genetic ancestry among a mixed population of NA and NHW women [17]. Results demonstrated that the pathway was overall statistically significant for breast cancer risk in women with low NA ancestry [17]. Eight of the 16 genes evaluated were associated with increased breast cancer risk (IL-1A, IL-1B, IL-1RN, IL-2, IL-2RA, IL-4, IL-6, IL-10); four genes were present in women with low NA ancestry (IL-1B, IL-6, IL-6R and IL-10) and two were associated with breast cancer risk among women with high NA ancestry (IL-2 and IL-2RA) [17]. These findings suggest that functional polymorphisms in IL genes influence the carcinogenic process [17]. Boone *et al.* examined the association of CYP19A1 single nucleotide polymorphisms (SNP) in NA breast cancer risk and mortality as genetic variation in the cytochrome p450 family 19 gene, *CYP19A1* has been linked to increased estrogen levels and aromatase expression [18]. Although there were no statistically significant association of SNP's with breast cancer risk or mortality, two SNPs were associated with increased breast cancer risk in women of moderate to high NA ancestry indicating that variation in *CYP19A1* may influence breast cancer risk differently in these women [18]. Chen *et al.* (2011) and Slattery *et al.* demonstrated that Ataxia Telangiectasia mutated gene ATM 5557G polymorphism and bone morphogenetic proteins (BMP) are associated with increased breast cancer risk in NA women [19,20].

Mortality and survival differences between NA and NHW women

Although breast cancer mortality rates have declined over the past two decades in NHW women, NA women are more likely to be diagnosed with late-stage breast tumors and experience a higher risk of mortality [21-24]. This mortality difference can be attributed to differences in tumor characteristics, stage at diagnosis, co morbidities and access, adherence, and response to treatments [25,26]. Additional factors like beliefs regarding screening and early detection, and negative attitudes about cancer treatment also contribute to this disparity [27]. Several genetic factors have also been known to influence breast cancer mortality in NA women. White *et al.* demonstrated that leptin signaling pathway and energy homeostasis genes were associated with breast cancer-specific mortality among women with low NA ancestry [28]. However, in the current study, cancer specific mortality was found to be almost equal between the 2 groups.

In regards to survival, five-year breast cancer survival rates for NA women are among the lowest of all racial/ethnic groups [29]. Pellatt *et al.* reported an association between *MAPK* genes and increased survival in women with low NA ancestry while White *et al* (2014) reported Neuropeptide Y (NPY) to influence breast cancer-specific survival among women with high NA ancestry only [28,30]. In the current study we found 1 year survival rates to be equal between the two groups whereas NA women had a lower mean overall survival and lower 5 year survival rates compared to NHW women.

Treatment and Screening among NA and NHW women

This higher mortality and lower survival rates as discussed above can be due to treatment and screening differences between the two groups. In this study, fewer NA women underwent surgery only compared to NHW women and a slightly higher number underwent combination surgery and radiation therapy. Similar findings were also reported in a retrospective study comparing cancer treatment between NA and NHW women by Javid *et al* [31]. According to this, NAs were less likely than NHW to receive primary surgical therapy, undergo recommended post-therapy surveillance and were also less likely to receive adjuvant chemotherapy or radiation therapy [31]. Misconceptions regarding cancer treatment among NA women have also been attributed to lower treatment rates [32].

Although the SEER database has no data on screening behavior, previous studies have shown that NA women have had the lowest mammography screening rates in the United States and screening rates have been declining since the year 2005 [33,34]. Indian Health Service (IHS) is the federal agency which provides health services to members of federally recognized tribes [30]. In the year 1990, the Breast and Cervical Cancer Mortality Prevention Act authorized the Centers for Disease Control and Prevention (CDC) to establish the National Breast and Cervical Cancer Early Detection Program (NBCCEDP), to provide breast and cervical cancer screening and diagnostic services to low-income, uninsured women and to fund American Indian and Alaska Native tribes and tribal organizations [30]. According to IHS data, in the year 2002, 42% of NA women aged 52-64 had a mammogram only once over a two year period [35]. In the year 2008, 62.7% of NA women aged 40 and older had a mammogram over a two year period, compared to 67.9% for NHW women [35]. Also between the years 2000 and 2008, screening mammography rates among NA women were among the lowest compared to women of other ethnic/racial groups and the percentage of NA women who were up to date with their biennial mammogram screening, were even lower [35,36]. In the last 2 years,

among women aged 40 and older, 63% of NA women had a mammogram compared to 66% of NHW women [37]. Prior studies have identified factors that limit screening outreach to NA women, which include lack of awareness regarding breast cancer, distance from the nearest healthcare facility, mistrust of professionals and poorly funded healthcare systems that have resulted in lowered community expectations for proper and timely cancer treatment and follow-up [36]. Also, there may be a generational divide in the way NA women perceive breast cancer and breast cancer screening. Older women consider screening mammography as embarrassing and humiliating [38]. There are indications that the perceptions of younger NA women toward breast cancer screening may be different from those of elders [39]. This was seen in a study where breast cancer was the leading cancer diagnosed and accounted for 30% of all cancers among young NA women aged 20–44 years across various IHS regions [39]. In order to improve screening rates, several programs like the Spirit of Eagles Community Networks Program (CNP) have demonstrated the effectiveness of personal navigators and/or Community Health Representatives in providing education and increasing cancer screening among NA women [40].

Limitations

There are several limitations of this study which must be taken into consideration. Data specific to NA women can be scarce due to variability among tribes and small numbers available for statistical analysis. It is also important to note the limitations of the SEER database inherent to large administrative databases, such as errors in coding and sampling, and lack of data concerning socioeconomic status. Secondly, information on diagnostic methods and follow up are lacking. Although data on surgical and radiation therapy were available in the SEER database; information on chemotherapy received was not, which limited this study's ability to evaluate the impact of adjuvant or neoadjuvant therapy which may have influenced survival. Additionally, data pertaining to cause of death in SEER comes from death certificates that are not verified independently, which can create some possibility of inaccuracy.

Summary

Racial disparities among breast cancer patients regarding disease outcomes have been well established in the literature over the last two decades. However, few data exist regarding the outcomes of disease exhibited by groups such as NA's. The current study demonstrates that, although NA women have a lower incidence of breast cancer compared to NHW women, they present more often with regional and distant stage of disease, poorly differentiated tumors and lymph node positive disease which can be attributed poor adherence to screening and hence diagnosis at a more advanced stage. The number of NA women undergoing surgery is slightly less than NHW women and majority of the women underwent surgery in combination with radiation therapy which could be due to lack of awareness, fears and cultural beliefs regarding treatment. NA women undergoing surgical resection have significantly prolonged survival compared to NHW women. Cancer specific mortality is slightly higher in NA women and 5 year survival rate is lower compared to NHW women. Limited genetic information is available on the NA female population and they should be encouraged to enroll into clinical trials to better understand their disease biology and improve overall treatment strategies.

Variables	Overall	Native American	Non-Hispanic white	p-value
N (%)	8,63,958	4,289 (0.5%)	859,669 (99.5%)	<0.01*
Under 20	74 (0.0%)	2 (0.0%)	72 (0.0%)	
20 to 39	44,462 (5.1%)	394 (9.2%)	44,068 (5.1%)	
40 to 59	329,786 (38.2%)	2,222 (51.8%)	327,564 (38.1%)	
60 to 79	376,779 (43.6%)	1,437 (33.5%)	375,342 (43.7%)	
80 and over	112,857 (13.1%)	234 (5.5%)	112,623 (13.1%)	

Abbreviations: N: number; SD: standard deviation; * statistically significant; NS: not statistically significant defined as $p > 0.05$

Table 1: Demographic profile of 863,958 patients with Breast Cancer from the Surveillance Epidemiology and End Result (SEER) Database (1973-2010).

Variables	Overall	Native American	Non-Hispanic white	p-value
N (%)	8,63,958	4,289 (0.5%)	859,669 (99.5%)	
Stage, N (%)*				< 0.001*
Localized	540,148 (62.5%)	2,509 (58.1%)	536,639 (62.5%)	
Regional	270,281 (31.3%)	1,450 (34.0%)	268,831 (31.3%)	
Distant	53,529 (6.2%)	330 (7.9%)	53,199 (6.1%)	
Tumor Size, N (%)*				NS*
Microscopic	1,900 (0.3%)	21 (0.5%)	1,879 (0.2%)	
Under 2 cm	487,824 (56.4%)	2,185 (50.9%)	485,639 (56.5%)	
2 to 4 cm	283,019 (32.9%)	1,510 (35.2%)	281,509 (32.9%)	
Over 4 cm	90,155 (10.4%)	573 (13.4%)	89,582 (10.4%)	
Grade, N (%)*				< 0.001*
Well differentiated	178,173 (20.6%)	780 (18.2%)	177,393 (20.6%)	
Moderately differentiated	365,785 (42.3%)	1,670 (38.9%)	364,115 (42.3%)	
Poorly differentiated	299,309 (34.7%)	1,732 (40.4%)	297,577 (34.6%)	
Undifferentiated	20,691 (2.5%)	107 (2.5%)	20,584 (2.5%)	
Lymph Node, N (%)*				NS*
Negative	579,762 (67.1%)	2,640 (61.6%)	577,122 (67.1%)	
Positive	284,196 (32.9%)	1,649 (38.4%)	282,547 (32.9%)	

Abbreviations: N: number; *data presented for patients with available information only; * statistically significant; NS: not statistically significant defined as $p > 0.05$.

Table 2: Tumor characteristics of 863,958 Patients with Breast Cancer from the Surveillance Epidemiology and End Result (SEER) Database (1973-2010).

Variables	Overall	Native American	Non-Hispanic white	p-value
N (%)	8,63,958	4289 (0.5%)	859,669 (99.5%)	
Treatment, N (%)*				NS*
No treatment	40,825 (4.9%)	234 (5.6%)	40,591 (4.9%)	
Radiation only	9696 (1.2%)	53 (1.3%)	9643 (1.2%)	
Surgery only	452,316 (54.3%)	2177 (52.5%)	450,139 (54.3%)	
Surgery and radiation	330,662 (39.7%)	1684 (40.6%)	328,978 (39.7%)	
Treatment-specific Survival (Years ± SD)*				NS*
No treatment		6.755 ± 1.184	5.609 ± 0.065	
Radiation only		3.767 ± 0.798	5.156 ± 0.112	
Surgery only		16.353 ± 0.459	15.650 ± 0.026	
Surgery and radiation		18.714 ± 0.627	18.821 ± 0.051	
Mean Overall Survival (years)	7.40 ± 6.69	6.66 ± 6.05	7.40 ± 6.69	< 0.001*
Overall Mortality, N (%)				< 0.001*
Alive	519,150 (60.1%)	2,773 (64.7%)	516,377 (60.1%)	
Dead	344,808 (39.9%)	1,516 (35.3%)	343,292 (39.9%)	
Cancer Specific Mortality, N (%)				< 0.001*
Alive	681,791 (78.8%)	3,357 (78.3%)	678,434 (78.8%)	
Cancer death	182,167 (21.2%)	932 (21.7%)	181,235 (21.2%)	
Cumulative survival, %				NS*
1-year		94.00%	94.00%	
2-year		89.00%	89.00%	
5-year		74.00%	76.00%	

Abbreviations: N: number; SD: standard deviation; *data presented for patients with available information only; * statistically significant; NS: not statistically significant defined as $p > 0.05$.

Table 3: Clinical outcomes of 863,958 Patients with Breast Cancer from the Surveillance Epidemiology and End Result (SEER) Database (1973-2010).

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