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REGIONAL DIFFERENCES IN BREAST CANCER BIOMARKERS IN AMERICAN INDIAN AND ALASKA NATIVE WOMEN

Judith S Kaur[1], **Robert A. Vierkant**[2], **Timothy Hobday**[1], and **Daniel Visscher**[3]
[1]Division of Medical Oncology, Mayo Clinic, Rochester, MN
[2]Department of Health Sciences Research, Mayo Clinic, Rochester, MN
[3]Division of Anatomical Pathology, Mayo Clinic, Rochester, MN

Abstract

Background/Rationale—Breast cancer is not a homogeneous disease, but several different and unique subtypes defined by gene expression analysis. Incidence and mortality rates vary by almost three fold between Alaska (highest) and the Southwestern tribes (lowest). We hypothesized that these differences may be due in part to varying levels of biologic tumor aggressiveness.

Methods—A bio-repository of the North Central Cancer Treatment Group with 95 cases of American Indian and Alaska Native women with adenocarcinoma of the breast surgically treated from 1990 to 2000 were tested for several biomarkers. Comparison distributions of biomarker values across state of residence using t-tests for continuous (p53, MIB-1, Cyclin D) and ordinally scaled markers (EGFR, BCL-2, Her2) and chi-square tests of significance for binary markers (ER, PR) were done.

Results—Significant regional differences in some biomarker expression levels were seen. No increase was observed in “triple negative” breast cancer or Her 2 overexpression in these cases.

Conclusions—Despite a three-fold difference in breast cancer mortality in Alaska Native vs. Southwestern American Indians, standard biomarkers such as ER, PR and Her 2 neu expression did not explain the disparity.

Impact—There is a need for research to understand the biologic basis of breast cancer disparities in AIAN women. Potential for a prospective trial will be explored with tribes.

Keywords

Breast cancer; biomarkers; American Indian/Alaska Native

Introduction

There has never been a prior pathologic series analyzing American Indian and Alaska Native breast cancer patterns. Breast cancer is a major cause of cancer mortality in American Indian and Alaska Native (AIAN) women. Previous studies had suggested that breast cancer rates are lower among AIAN women than among women of other racial and ethnic groups (1–6). However, breast cancer survival among AIAN women reportedly was lower than among non-Hispanic White women in SEER registry areas. The Spirit of Eagles Community

Corresponding Author: Judith S. Kaur, Mayo Clinic, 200 1st St. SW, Rochester, MN 55905, kaur.judith@mayo.edu, phone 507-284-8432, Fax 507-284-1803.

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Networks Program (CNP) (CNP U01 153604 and U54 153605) is the only national CNP working for more than a decade with American Indians and Alaska Natives on cancer prevention and control. The Principal Investigator for that CNP was a co-author on data published in 2008 that show striking regional differences in breast cancer incidence with lowest rates in Arizona and highest in Alaska with almost a threefold difference in incidence and mortality between the two states (1). The female breast cancer incidence rate in Alaska was 134.8/100,000 vs. 50.8/100,000 in the Southwest from 1999–2004, the most recent complete data published.

We hypothesized that these differences may be due in part to varying levels of biologic tumor aggressiveness. A bio-repository of paraffin embedded breast cancer tumors was created as collaboration between the North Central Cancer Treatment Group and the Spirit of E.A.G.L.E.S. CNP as a special project.

Breast cancer is not a homogeneous disease but a compilation of several different and unique subtypes defined by gene expression analysis. AIAN are rarely included in reviews of breast cancer. For example, differences in breast cancer hormone receptor status and histology by race and ethnicity among women 50 years of age and older was found in 11 population-based cancer registries connected with the SEER Program. Significantly that review did not include American Indians and Alaska Natives because of small sample size for this population in the registries (7).

Epidemiologic features found in the Carolina Breast Cancer Study (8), a population-based, case-control study analyzed clinical associations showed African American women had a high prevalence of basal-like tumors, particularly among premenopausal women. The observation that so-called “triple-negative breast cancers” (ER-, PR- and Her2-) had worse prognosis has led to more attention to the molecular classification and forecasting for breast cancer (9). Other markers have been reputed to provide prognostic and predictive value in breast cancer patients and were analyzed in a panel of biomarkers (9–37) described in Table 1.

We hypothesized that observed regional differences in breast cancer incidence and mortality in AIAN populations might also reflect underlying molecular biologic differences. This retrospective study is the first such evaluation of a significant number of American Indian and Alaska Native breast cancer patients from a bio-repository established to analyze these two regions with widely different incidence and survival rates. These cases were not enrolled in clinical trials and were accrued as a special project of the NCCTG and Spirit of E.A.G.L.E.S. CNP in conjunction with tribes across the country.

MATERIALS AND METHODS

The Study Population

All American Indian and Alaska Native women with primary adenocarcinoma of the breast surgically treated and with available paraffin-embedded tissue from 1990 to 2000 from the Phoenix Area of the Indian Health Service and the Alaska Native Medical Center were eligible for inclusion in this retrospective study. Those years were chosen by the tribal IRBs since the blocks were allowed to be stored permanently. All data reported here is aggregate and de-identified. Blocks could be returned to the pathologist if clinically required for treatment decisions for patients with late relapses.

A separate protocol at the Phoenix Indian Medical Center allowed for demographic data not present in the pathology reports to be abstracted from the clinical records by a nurse practitioner. That data is also presented in a table in aggregate format. (Table 2)

A small number of cases (total of 16 cases) from North Dakota and South Dakota were initially also accrued but because the pathology labs were outside of the Indian Health system, complete pathology and clinical correlates could not be released due to hospitals in those states concerned about HIPAA compliance.

Registration Procedures

IRB approval letters from the Phoenix Area Indian Health Service and Alaska Area were provided before pathologic review. Registration of the materials was done via the Materials Library maintained by the NCCTG Research pathology coordinator. The bio-repository tissues are stored per protocol in a secure area within the NCCTG Central Operations Office. Information regarding age and stage of these patients were abstracted from pathology reports.

Tissue Processing

Paraffin blocks were recut at the Mayo Clinic Pathology Department in 5 micron slices and reviewed for standard pathologic features. New sections were cut for the panel of molecular markers and interpreted by a board certified pathologist.

The panel of molecular markers that could be performed on paraffin imbedded specimens was selected based on literature review of their prognostic significance. Retrospective analysis of tissue blocks measured expression levels for the following panel of biomarkers: ER and PR (coded as positive vs. negative); her2, BCL-2, and EGFR (ordinally scaled as 0, 1+, 2+, and 3+) and P53, MIB-1 and Cyclin D (continuous percent of cells stained).

Statistical Methods

The overall objective of these analyses was to determine whether cancer-related biomarkers differ between Native American breast cancer cases residing in Alaska and those residing in Arizona. Data were descriptively summarized using means and standard deviations for continuous and ordinal variables, and frequencies and percents for binary variables. We compared distributions of biomarker values across state of residence using t-tests for continuous markers (p53, MIB-1, Cyclin D1) and chi-square tests of significance for binary markers (ER, PR). The ordinally scaled markers (EGFR, BCL-2, HER2) were also examined using t-tests to take into account the inherent ordering of the values, under the biological assumption that observed associations, if any, would exhibit a dose-response pattern with state of residence. Due to the small number of subjects in some groups, two sets of analyses were carried out: one based on the usual testing techniques that rely upon asymptotic assumptions, and one using non-parametric randomization tests that are robust to deviations from these assumptions(38). For these latter analyses, a standard t-test or chi-square test was run, and a test statistic calculated, on the observed data. Next, subject-specific state or village residency was randomly shuffled to simulate the null hypothesis, and a t-test or chi-square test was run on the resulting data set. This reshuffling step was repeated 10,000 times to generate an empirical distribution of test statistics under the null hypothesis (39). The test statistic based on the observed data was then compared to this empirical distribution, and a final randomization test p-value was calculated as the proportion of the null hypothesis test statistics that were more extreme than the observed one.

Many of the biomarkers of interest, such as ER and PR, are known to differ according to age. To rule out the possibility that the observed association between a given biomarker and residency was due to the confounding effects of age, we ran a series of age-adjusted analyses using analyses of covariance for continuous and ordinal variables and logistic regression models for binary variables. Two such sets of analyses were run: one for age and one for tumor stage. For each, we first subset subjects with non-missing values for the

covariate of interest. We then fit models both before and after covariate adjustment and compared results. All statistical tests were two-sided, and all analyses were carried out using the SAS (SAS Institute, Inc. Cary, NC) software system.

RESULTS

A total of 95 breast cancer cases were included in the study: 53 from Arizona and 42 from Alaska. Mean age at diagnosis and the percentage of high stage tumors (i.e. stage 3 or 4) were similar across state of residence (Table 2).

Molecular characteristics

Cases from AK had higher levels of p53 staining (40.3 vs. 18.5, p=0.004) and lower levels of both EGFR (mean ordinal scaling 0.15 vs. 0.53, p=0.02) and Her2 (mean ordinal scaling 0.81 vs. 1.32, p=0.02) than those from AZ. No differences in distribution were observed for MIB-1, Cyclin D, BCL-2, ER or PR. When examined together, the triple negative combination of ER/PR/Her2 also did not differ across states (12% for AK vs. 13% for AZ, p=0.85). (Table 3) Non-parametric Monte Carlo based randomization tests and age- and stage-adjusted analyses yielded similar associations to those presented in Table 1 (data not shown).

DISCUSSION

This is the first study to compare American Indian and Alaska Native women with breast cancer in regions with markedly distinctive patterns of incidence and mortality. We began this study to develop a tissue repository of AIAN breast cancer cases at a time when there was suspicion that breast cancer rates were rising. The data had not been analyzed until the Wingo (1) article appeared in a special report. Our study also began before the recognition of distinctive biomarker patterns such as “triple negative” breast cancer. This study did not have the luxury of the newer technology such as Oncotype Dx for defining those marker patterns (36). However, the relative contributions of standard clinical features such as immunohistochemical analysis of ER, PR, HER2 and Ki-67 in the absence of a controlled clinical trial are the most commonly used clinicopathologic assessment tools to predict recurrence (40).

We hypothesized that there might be differences in biomarker patterns of these breast cancers. We were particularly interested in finding out if there was a preponderance of either triple negative or Her2 positive cancers to explain these observations. However, neither of these patterns appears to explain the differences observed. Unfortunately there are very small numbers of American Indians and Alaska Natives in clinical trials, so only this retrospective review of molecular patterns was possible. In the absence of a clinical trial, data presented here is limited by the retrospective nature of the acquisition of paraffin embedded tissues. Alaska and Arizona were selected because most of the samples were able to be accessed through IRB agreements with tribal health boards in those states. Alaska is a SEER special registry as well. While we identified cases of breast cancer tissues from AI women in North Dakota and South Dakota, the pathology departments of many small hospitals were unwilling to send specimens due to their interpretation of HIPAA compliance. We found that regional differences in biomarker expression levels of P53, EGFR and HER2 may exist in AIAN women. While stage of disease would certainly affect mortality rates, the most comprehensive review of regional patterns of breast cancer in AIAN women found no difference in early vs. late stages of breast cancer in Alaska vs. the Southwest. However more Southwestern women had higher rates of being “unstaged”(1). Our staging data on the cases included in this review confirmed staging patterns previously reported. A new review of incidence and mortality patterns of breast cancer in AIAN women

will be published in 2013 but unfortunately no data on the molecular markers of interest will be in that report (48). The current mortality data still confirms the dramatic regional differences in breast cancer seen in AK and AZ.

Currently, there are no data on genetic testing for BRCA1, BRCA2 in these populations. There are no genetic counselors within the Indian Health System and referrals for treatment to oncologists in private practice or academic health centers may not include or approve this service. Therefore studies of genetic association with breast cancer risk are quite limited for AIAN women. There are families where breast and ovarian cancer have been noted and there are other hereditary forms of cancer such as Lynch Syndrome documented in some tribes. While controversial, there is mixed evidence that breast cancer should be included in Lynch Syndrome. (49–52). No genetic information was available to evaluate for this study but it is unlikely that the three fold incidence and mortality rates between AK and AZ would be explained by heritable disease. We do note that the self-reported rate of first degree relatives with breast cancer is around 8 percent in both regions included in this study (53), which is quite similar to the general United States population. The higher percentage of AIAN women diagnosed before age 50 (30 percent [30.6 vs. 16.3 in NHW]) underscores the importance of providing culturally appropriate counseling about the value of genetic testing. Excess mortality from breast cancer in the 40–50 year old group of AIAN women requires more research and interventions that are scientifically and culturally appropriate. The genetic influence on breast cancer incidence and mortality in this study is unknown.

Certainly, there are many plausible explanations for the differences in AZ and AK such as screening rates and delay from diagnosis to treatment. A recent review of breast cancer in low income women showed a significant survival difference with delay in treatment for advanced stage patients greater than 60 days from diagnosis. (54). We do not know the time from diagnosis to treatment for this patient group. There other limitations to this study including small numbers and treatment details. Many issues relate to the fragmented care for AIAN cancer patients. A woman may have her mammogram in one location, biopsy in another, definitive surgery elsewhere and systemic therapy in yet another facility. Any future studies will need to overcome these obstacles in order to paint a clear biologic and clinical picture of breast cancer in this population. AI women in Arizona are more likely to present with a palpable mass and higher stages of breast cancer than other racial or ethnic groups. (Table 4) Chart review data was only available for Arizona due to IRB restrictions in Alaska.

We hope that future studies will find this pattern changing. The late stage diagnoses can only be reduced with new and innovative approaches tailored to increase mammographic or other appropriate screening among high risk women in the AIAN population. The U.S. Preventive Services Task Force recommends only biennial screening mammography in women aged 50 to 74 years old. The decision to start regular, biennial screening mammography “before the age of 50 years should be an individual one and take patient context into account, including the patient’s values regarding specific benefits and harms” (55) There is no uniformity within the Indian Health System about referral for mammography. This group of women has had less access to screening mammography historically. The latest reports from the Indian Health Service in 2009 reported that the percentage of women ages 52–64 who had mammography screening in the prior two years was only 45 percent. It specifically noted that although there has been overall improvement in breast cancer mortality rates in the general population, “AIAN women have not shared these gains”(56).

In summary, we found differing patterns of p53, EGFR and Her2 tumor expression in AIAN breast cancer cases from Alaska compared to those from Arizona (Figure 1). These

differences may explain some, but likely not all, of the previously observed differences in breast cancer mortality in AIAN populations. Understanding the excess burden of breast cancer in AIAN populations will require further research to confirm and expand our results and determine to what extent observed biomarker differences may explain known differences in mortality.

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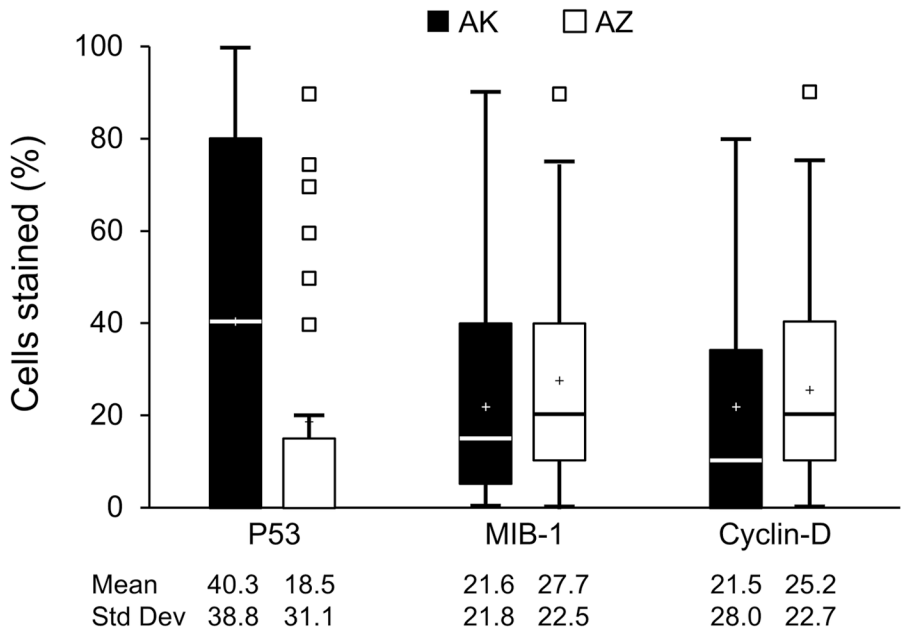

Figure 1.

Boxplots of continuous biomarker values by state. Values represent percent of cells that stained positive for the biomarker of interest. Upper and lower borders of the box represent the 75th and 25th percentiles, respectively. Median and mean values are represented by the blue line inside the box and plus sign, respectively. Whiskers represent the range of values contained within 1.5 times the width of the inter-quartile range above and below the 75th and 25th percentiles. Small boxes represent values lying outside borders of the whiskers.

Table 1

SELECT BIOMARKERS OF BREAST CANCER PROGNOSIS

Marker	Impact	References
BCL-2/BAX	Promotes cell death	10, 11, 12
EGFR/HER1	Overexpressed in triple negative tumors	13, 38–44
P53	Mutation associated with poor prognosis	14–24,
MIB-1/Ki-67	Proliferation index	26–35
Cyclin D	Regulates cell cycle	37, 44–47

Table 2

Demographic and clinical variables by state of residency

Attribute	Alaska	Arizona
Age: Mean (N, SD)	55.2 (42, 9.2)	58.3 (52, 14.4)
Tumor Stage: N (%)		
0	1 (2)	1 (2)
1	16 (39)	12 (30)
2	18 (44)	17 (42)
3	5 (12)	2 (5)
4	1 (2)	8 (20)

SD, standard deviation; N, number of subjects with non-missing values; %, percent of subjects with tumor stage of interest in a given state of residence.

Table 3

Associations between biomarkers of interest and state of residency

Biomarker	Alaska (N=42)	Arizona (N=53)	P-value[4]
Continuous Markers[1]			
P53	40.3 (38.8)	18.5 (31.1)	0.004
MIB-1	21.6 (21.8)	27.7 (22.5)	0.190
Cyclin D1	21.5 (28.0)	25.3 (22.7)	0.476
Ordinal Markers[2]			
EGFR	0.15 (0.58)	0.53 (0.82)	0.015
BCL-2	2.07 (1.30)	2.17 (1.07)	0.686
HER2	0.81 (1.13)	1.32 (1.01)	0.023
Binary Markers[3]			
ER			0.722
Negative	9 (21)	13 (25)	
Positive	33 (79)	40 (75)	
PR			0.095
Negative	12 (29)	24 (45)	
Positive	30 (71)	29 (55)	
HER2 (2 or 3+)			0.087
Negative	33 (79)	33 (62)	
Positive	9 (21)	20 (38)	
HER2 (3+)			0.968
Negative	35 (83)	44 (83)	
Positive	7 (17)	9 (17)	
ER/PR/HER2 (2 or 3+)			0.930
Triple Negative	5 (12)	6 (11)	
Positive	37 (88)	47 (89)	
ER/PR/HER2 (3+)			0.849
Triple Negative	5 (12)	7 (13)	
Positive	37 (88)	46 (87)	

[1] Values for continuous markers are based on percent staining and range from 0 to 100. Summary statistics provided are mean (standard deviation).

[2] Values for ordinal markers are based on staining intensity and take on values of 0, 1, 2, or 3. Summary statistics provided are mean (standard deviation).

[3] Binary markers are classified as negative or positive. Summary statistics provided are Number positive (percent).

[4] Unadjusted p-value from two-sample t-test (for continuous or ordinal markers) or chi-square test (for binary markers). Age-adjusted analyses and randomization tests yielded similar results.

Table 4

Demographic and Clinical Characteristics for 50 Native American Breast Cancer Cases from Arizona.

Attribute	N (%)
Menopausal status	
Pre-menopausal	14 (28)
Post-menopausal	32 (64)
Unknown	4 (8)
Family history of breast cancer	
None	38 (76)
First degree relative	4 (8)
More distant relative	3 (6)
Unknown	5 (10)
Smoking status	
Never	33 (66)
Ever	12 (24)
Unknown	5 (10)
Use of exogenous estrogens	
Never	32 (64)
Ever	13 (26)
Unknown	5 (10)
Previous breast biopsy	
No	33 (66)
Yes	9 (18)
Unknown	8 (16)
Clinical presentation	
Mass	37 (74)
Mammogram	10 (20)
Radical mastectomy	1 (2)
Unknown	2 (4)
Local therapy	
Biopsy only	1 (2)
Lumpectomy only	3 (6)
Lumpectomy plus nodal dissection	16 (32)
Mastectomy only	4 (8)
Unknown	23 (46)
	3 (6)