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Research Article

Regional Differences in Breast Cancer Biomarkers in American Indian and Alaska Native Women

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Abstract

Background: 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 3-fold between Alaska (highest) and the Southwestern tribes (lowest). We hypothesized that these differences may be due to, in part, varying levels of biologic tumor aggressiveness.

Methods: A biorepository of the North Central Cancer Treatment Group with 95 cases of American Indian and Alaska Native (AIAN) women with adenocarcinoma of the breast surgically treated from 1990 to 2000 was 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 [EGF receptor (EGFR), BCL-2, Her2] and χ^2 tests of significance for binary markers [estrogen receptor (ER), progesterone receptor (PR)] were done.

Results: Significant regional differences in some biomarker expression levels were seen. No increase was observed in "triple-negative" breast cancer or Her2 overexpression in these cases.

Conclusions: Despite a 3-fold difference in breast cancer mortality in Alaska Native versus Southwestern American Indians, standard biomarkers such as ER, PR, and Her2 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.

See all articles in this *CEBP* Focus section, "Community Network Program Centers."

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Introduction

There has never been a prior pathologic series analyzing American Indian and Alaska Native (AIAN) breast cancer patterns. Breast cancer is a major cause of cancer mortality in 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 (NHW) women in Surveillance Epidemiology and End Results (SEER) registry areas. The Spirit of E.A.G.L.E.S Community Networks Program (CNP; CNP U01 153604 and U54 153605) is the only national CNP working for more than a decade with AIAN on cancer prevention and control. The principal investigator for that CNP was a coauthor 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 3-fold difference in incidence and mortality between the two states (1). The female breast cancer incidence rate in Alaska was 134.8/100,000 versus 50.8/100,000 in the Southwest from 1999–2004, the most recent complete data published.

We hypothesized that these differences may be due to, in part, varying levels of biologic tumor aggressiveness. A biorepository of paraffin-embedded breast cancer tumors was created as collaboration between the North Central Cancer Treatment Group (NCCTG) 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. AIANs 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 AIANs 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 that African American women had a high prevalence of basal-like tumors, particularly among premenopausal women. The observation that so-called "triple-negative breast cancers" [estrogen receptor negative (ER^-), progesterone receptor negative (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

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Table 1. Select biomarkers of breast cancer prognosis

Marker	Impact	References
BCL-2/BAX	Promotes cell death	10–12
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, 44–46

reputed to provide prognostic and predictive value in patients with breast cancer 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 AIAN patients with breast cancer from a biorepository 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 AIAN 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 Institutional Review Board (IRB) because the blocks were allowed to be stored permanently. All data reported here are aggregate and deidentified. 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 (Phoenix, AZ) allowed for demographic data not present in the pathology reports to be abstracted from the clinical records by a nurse practitioner. Those data are 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 laboratories were outside of the Indian Health system, complete pathology and clinical correlates could not be released because of hospitals in those states concerned about Health Insurance Portability and Accountability Act (HIPPA) 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 biorepository tissues are stored per protocol in a secure area within the NCCTG Central Operations Office. Information about age and stage of these patients were abstracted from pathology reports.

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)

Abbreviations: *N*, number of subjects with nonmissing values; %, percentage of subjects with tumor stage of interest in a given state of residence.

Tissue processing. Paraffin blocks were recut at the Mayo Clinic Pathology Department (Rochester, MN) in 5-μm 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 on the basis of 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 EGF receptor (EGFR; ordinally scaled as 0, 1+, 2+, and 3+) and P53, MIB-1, and cyclin D (continuous percentage of cells stained).

Statistical analysis

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 SDs for continuous and ordinal variables, and frequencies and percentages 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 χ^2 tests of significance for binary markers (ER and 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 biologic assumption that observed associations, if any, would exhibit a dose–response pattern with state of residence. Because of 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 nonparametric randomization tests that are robust to deviations from these assumptions (38). For these latter analyses, a standard t test or χ^2 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 χ^2 test was run on the resulting dataset. 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 with 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 nonmissing values for the covariate of interest. We then fit models both before and after covariate adjustment and compared the results. All statistical tests were two sided, and all analyses were carried out using the SAS (SAS Institute, Inc.) 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 III or IV) were similar across the state of residence (Table 2).

Molecular characteristics

Cases from Alaska 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 Arizona. 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 Alaska vs. 13% for Arizona, $P = 0.85$; Table 3). Nonparametric Monte Carlo-based randomization tests and age- and stage-adjusted analyses yielded similar associations to those presented in Table 1 (data not shown).

Table 3. Associations between biomarkers of interest and state of residency

Biomarker	Alaska ($N = 42$)	Arizona ($N = 53$)	P[d]
Continuous markers[a]			
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[b]			
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[c]			
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)	

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

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

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

[d]Unadjusted P value from two-sample t test (for continuous or ordinal markers) or χ^2 test (for binary markers). Age-adjusted analyses and randomization tests yielded similar results.

Discussion

This is the first study to compare AIAN 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 and colleagues' (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 whether there was a preponderance of either triple-negative or Her2-positive cancers to explain these observations. However, neither of these patterns seems to explain the differences observed. Unfortunately, there are very small numbers of AIANs in clinical trials, so only this retrospective review of molecular patterns was possible. In the absence of a clinical trial, data presented here are 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. Although we identified cases of breast cancer tissues from American Indian 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. Although 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 versus late stages of breast cancer in Alaska versus 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 (47). The current mortality data still confirm the dramatic regional differences in breast cancer seen in Alaska and Arizona.

Currently, there are no data on genetic testing for BRCA1 and 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. Although controversial, there is mixed evidence that breast cancer should be included in Lynch syndrome (48–51). No genetic information was available to evaluate for this study but it is unlikely that the 3-fold incidence and mortality rates between Alaska and Arizona would be explained by heritable disease. We do note that the self-reported rate of first-degree relatives with breast cancer is around 8% in both regions included in this study (52), which is quite similar to the general United States population. The higher percentage of AIAN women diagnosed before the age of 50 years [30% (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- to 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 Arizona and Alaska 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 more than 60 days from diagnosis (53). We do not know the time from diagnosis to treatment for this patient group. The other limitations to this study included small numbers and treatment details. Many issues relate

Table 4. Demographic and clinical characteristics for 50 Native American breast cancer cases from Arizona

Attribute	*N* (%)
Menopausal status	
Premenopausal	14 (28)
Postmenopausal	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)

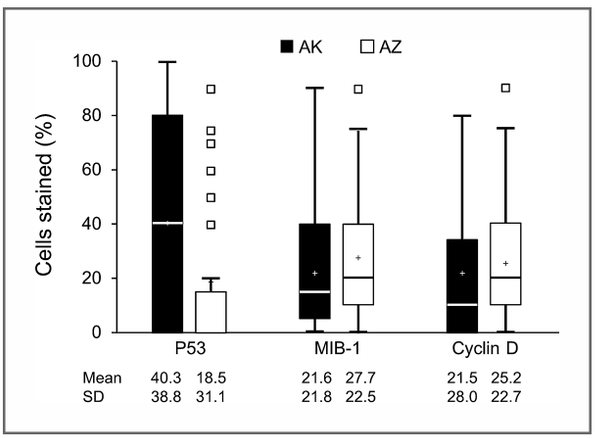

Figure 1. Boxplots of continuous biomarker values by state. Values represent percentage of cells that stained positive for the biomarker of interest. Top and bottom borders of the box represent the 75th and 25th percentiles, respectively. Median and mean values are represented by the line inside the box and plus sign, respectively. Whiskers represent the range of values contained within 1.5 times the width of the interquartile range above and below the 75th and 25th percentiles. Small boxes represent values lying outside borders of the whiskers.

to the fragmented care for AIAN patients with cancer. A woman may have her mammogram in one location, biopsy in another, definitive surgery elsewhere, and systemic therapy in yet another facility. Any future study will need to overcome these obstacles to paint a clear biologic and clinical picture of breast cancer in this population. American Indian 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 were 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 ages 50- to 74-year-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 about specific benefits and harms" (54). 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 to 64 years who had mammography screening in the prior 2 years was only 45%. 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" (55).

In summary, we found differing patterns of p53, EGFR, and Her2 tumor expression in AIAN breast cancer cases from Alaska compared with those from Arizona (Fig. 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.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.S. Kaur
Development of methodology: J.S. Kaur, R.A. Vierkant, D.W. Visscher
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.S. Kaur, T.J. Hobday, D.W. Visscher
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.S. Kaur, R.A. Vierkant, D.W. Visscher
Writing, review, and/or revision of the manuscript: J.S. Kaur, R.A. Vierkant, T.J. Hobday
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.S. Kaur
Study supervision: J.S. Kaur

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References

1. Wingo PA, King J, Swan J, Coughlin SS, Kaur JS, Erb Alvarez JA, et al. Breast cancer incidence among American Indian and Alaska Native women: US, 1999–2004. Cancer 2008;113(5 Suppl):1191–202.
2. Espey D, Paisano R, Cobb N. Regional patterns and trends in cancer mortality among American Indians and Alaska Natives, 1990–2001. Cancer 2005;103:1045–53.
3. Cobb N, Paisano RE. Patterns of cancer mortality among Native Americans. Cancer 1998;83:2377–83.
4. Hebert JR, Daguise VG, Hurley DM, Wilkerson RC, Mosley CM, Adams SA, et al. Mapping cancer mortality-to-incidence ratios to illustrate racial and sex disparities in a high-risk population. Cancer 2009;115:2539–52.
5. Espey DK, Wu XC, Swan J, Wiggins C, Jim MA, Ward E, et al. Annual report to the nation on the status of cancer, 1975-2004, featuring cancer in American Indians and Alaska Natives. Cancer 2007;110:2119–52.
6. Li CI, Malone KE, Daling JR. Differences in breast cancer stage, treatment, and survival by race and ethnicity. Arch Intern Med 2003;163:49–56.
7. Li CI, Malone KE, Daling JR. Differences in breast cancer hormone receptor status and histology by race and ethnicity among women 50 years of age and older. Cancer Epidemiol Biomarkers Prev 2002;11:601–7.

8. Anders CK, Carey LA. Biology, metastatic patterns, and treatment of patients with triple-negative breast cancer. Clin Breast Cancer 2009;9 Suppl 2:S73–81.
9. Brenton JD, Carey LA, Ahmed AA, Caldas C. Molecular classification and molecular forecasting of breast cancer: ready for clinical application? J Clin Oncol 2005;23:7350–60.
10. Reed JC. Regulation of apoptosis by bcl-2 family proteins and its role in cancer and chemoresistance. Curr Opin Oncol 1995;7: 541–6.
11. Joensuu H, Pylkkänen L, Toikkanen S. Bcl-2 protein expression and long-term survival in breast cancer. Am J Pathol 1994;145:1191–8.
12. Johnston SR, MacLennan KA, Sacks NP, Salter J, Smith IE, Dowsett M. Modulation of Bcl-2 and Ki-67 expression in oestrogen receptor-positive human breast cancer by tamoxifen. Eur J Cancer 1994; 30A:1663–9.
13. Baselga J, Gomez P, Greil R, Braga S, Climent MA, Wardley AM, et al. Randomized phase II study of the anti-epidermal growth factor receptor monoclonal antibody cetuximab with cisplatin versus cisplatin alone in patients with metastatic triple-negative breast cancer. J Clin Oncol 2013;31:2586–92.
14. Eeles RA. Predictive testing for germline mutations in the p53 gene: are all the questions answered? Eur J Cancer 1993;29A:1361–5.
15. Eeles RA, Bartkova J, Lane DP, Bartek J. The role of TP53 in breast cancer development. Cancer Surv 1993;18:57–75.
16. Eeles RA. Germline mutations in the TP53 gene. Cancer Surv 1995;25:101–24.
17. Hollstein M, Hainaut P. Massively regulated genes: the example of TP53. J Pathol 2010;220:164–73.
18. Hollstein M, Hergenhahn M, Yang Q, Bartsch H, Wang ZQ, Hainaut P. New approaches to understanding p53 gene tumor mutation spectra. Mutat Res 1999;431:199–209.
19. Hollstein M, Moeckel G, Hergenhahn M, Spiegelhalder B, Keil M, Werle-Schneider G, et al. On the origins of tumor mutations in cancer genes: insights from the p53 gene. Mutat Res 1998;405:145–54.
20. Hollstein M, Bartsch H, Wesch H, Kure EH, Mustonen R, Mühlbauer KR, et al. p53 gene mutation analysis in tumors of patients exposed to alpha-particles. Carcinogenesis 1997;18:511–6.
21. Hollstein M, Soussi T, Thomas G, von Brevern MC, Bartsch. P53 gene alterations in human tumors: perspectives for cancer control. Recent Results Cancer Res 1997;143:369–89.
22. Hollstein M, Shomer B, Greenblatt M, Soussi T, Hovig E, Montesano R, et al. Somatic point mutations in the p53 gene of human tumors and cell lines: updated compilation. Nucleic Acids Res 1996; 24:141–6.
23. Hollstein M, Rice K, Greenblatt MS, Soussi T, Fuchs R, Sørlie T, et al. Database of p53 gene somatic mutations in human tumors and cell lines. Nucleic Acids Res 1994;22:3551–5.
24. Hollstein M, Sidransky D, Vogelstein B, Harris CC. p53 mutations in human cancers. Science 1991;253:49–53.
25. Malkin D. Li-fraumeni syndrome. Genes Cancer 2011;2:475–84.
26. Cattoretti G, Becker MH, Key G, Duchrow M, Schlüter C, Galle J, et al. Monoclonal antibodies against recombinant parts of the Ki-67 antigen (MIB 1 and MIB 3) detect proliferating cells in microwave-processed formalin-fixed paraffin sections. J Pathol 1992;168:357–63.
27. Wintzer HO, Zipfel I, Schulte-Mönting J, Hellerich U, von Kleist S. Ki-67 immunostaining in human breast tumors and its relationship to prognosis. Cancer 1991;67:421–8.
28. Sahin AA, Ro JY, Brown RW, Ordonez NG, Cleary KR, el-Naggar AK, et al. Assessment of Ki-67-derived tumor proliferative activity in colorectal adenocarcinomas. Mod Pathol 1994;7:17–22.
29. Sahin AA, Ro JY, el-Naggar AK, Wilson PL, Teague K, Blick M, et al. Tumor proliferative fraction in solid malignant neoplasms. a comparative study of Ki-67 immunostaining and flow cytometric determinations. Am J Clin Pathol 1991;96:512–9.
30. Sahin AA, Ro J, Ro JY, Blick MB, el-Naggar AK, Ordonez NG, et al. Ki-67 immunostaining in node-negative stage I/II breast carcinoma. Significant correlation with prognosis. Cancer 1991;68:549–57.
31. Veronese SM, Maisano C, Scibilia J. Comparative prognostic value of Ki-67 and MIB-1 proliferation indices in breast cancer. Anticancer Res 1995;15(6B):2717–22.
32. Thor AD, Liu S, Moore DH II, Edgerton SM. Comparison of mitotic index, in vitro bromodeoxyuridine labeling, and MIB-1 assays to quantitate proliferation in breast cancer. J Clin Oncol 1999;17: 470–7.
33. Clahsen PC, van de Velde CJ, Duval C, Pallud C, Mandard AM, Delobelle-Deroide A, et al. The utility of mitotic index, oestrogen receptor and Ki-67 measurements in the creation of novel prognostic indices for node-negative breast cancer. Eur J Surg Oncol 1999;25: 356–63.
34. Urruticoechea A, Smith IE, Dowsett M. Proliferation marker Ki-67 in early breast cancer. J Clin Oncol 2005;23:7212–20.
35. de Azambuja E, Cardoso F, de Castro G Jr, Colozza M, Mano MS, Durbecq V, et al. M. Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12,155 patients. Br J Cancer 2007;96:1504–13.
36. Tang G, Shak S, Paik S, Anderson SJ, Costantino JP, Geyer CE Jr, et al. Comparison of the prognostic and predictive utilities of the 21-gene Recurrence Score assay and Adjuvant! for women with node-negative, ER-positive breast cancer: results from NSABP B-14 and NSABP B-20. Breast Cancer Res Treat 2011; 127:133–42.
37. Naidu R, Wahab NA, Yadav MM, Kutty MK. Expression and amplification of cyclin D1 in primary breast carcinomas: relationship with histopathological types and clinico-pathological parameters. Oncol Rep 2002;9:409–16.
38. Zhang X, Meng J, Wang ZY. A switch role of Src in the biphasic EGF signaling in ER-negative breast cancer cells. PLoS ONE 2012;7: e61613.
39. Manly BJF. Randomization, bootstrap, and Monte Carlo methods in biology, third edition. Boca Raton, FL: Chapman & Hall/CRC; 2007. p. 81–90.
40. Lundin SH, Lundin M, Lehtimaki T, Ristimaki A, Holli K, Sailas L, et al. Breast cancer biological subtypes and protein expression predict for the preferential distant metastasis sites: a nationwide cohort study. Breast Can Res 2011;13:R87.
41. Tunca B, Egeli U, Cecener G, Tezcan G, Gokgoz S, Tasdelen I, et al. CK19, CK20, EGFR and HER2 status of circulating tumor cells in patients with breast cancer. Tumori 2012;98:243–51.
42. Chen SJ, Luan J, Zhang HS, Ruan CP, Ku KY, Li QQ, et al. EGFR-mediated G1/S transition contributes to the multidrug resistance in breast cancer cells. Mol Biol Rep 2012;39:5465–71.
43. Nakagawa M, Bando Y, Nagao T, Takai C, Ohnishi T, Honda J, et al. Among triple-negative breast cancers, HER2(0) breast cancer shows a strong tendency to be basal-like compared with HER2 (1+) breast cancer: preliminary studies. Breast Cancer 2012; 19:54–9.
44. Niwinska A, Olszewski W, Murawska M. Pogoda K. Triple-negative breast cancer with brain metastases: a comparison between basal-like and non-basal-like biological subtypes. J Neuro Oncol 2011;105: 547–53.
45. Musgrove EA, Lee CSL, Buckley MF, Sutherland RL. Cyclin D1 induction in breast cancer cells shortens G_1 and is sufficient for cells arrested in G_1 to complete the cell cycle. Proc Natl Acad Sci U S A 1994;91:8022–26.
46. Keyomarsi K, Tucker SL, Buchholz TA, Callister M, Ding Y, Hortobagyi GN, et al. Cyclin E and survival in patients with breast cancer. New Engl J Med 2002;347:1566–75.
47. White A, Richardson L, Kaur JS, Li C, Ekwueme DU. Breast Cancer Mortality among American Indian/Alaskan Natives, 1990—2009; Am J Public Health 2013, in press.
48. Pande M, Wei C, Chen J, Amos CI, Lynch PM, Lu KH, et al. Cancer spectrum in DNA mismatch repair gene mutation carriers: results from a hospital based Lynch syndrome registry. Fam Cancer 2012;11: 441–7.
49. Grandval P, Barouk-Simonet E, Bronner M, Buisine MP, Moretta J, Tinat J, et al. Is the controversy on breast cancer as part of the Lynch-related tumor spectrum still open? Fam Cancer 2012;11: 681–3.
50. Aung KW, Lindor NM, Jenkins MA. Risk of breast cancer in Lynch syndrome: a systematic review. Breast Cancer Res 2013,15:R27.

51. Lotsari JE, Gylling A, Abdel-Rahman WM, Nieminen TT, Aittomaki K, Friman M, et al. Breast carcinoma and Lynch syndrome: molecular analysis of tumors arising in mutation carriers, non-carriers, and sporadic cases. Breast Cancer Res 2012;14:R90
52. Kaur JS, Roubidoux MA, Sloan J, Novotny P. Can the Gail Model be useful in American Indian and Alaska Native populations? Cancer 2004;100:906–12.
53. McLaughlin JM, Anderson RT, Ferketich AK, Seiber EE, Balkrishnan R, Paskett ED. Effect on survival of longer intervals between confirmed diagnosis and treatment initiation among low-income women with breast cancer. J Clin Oncol 2012;30:4493–500.
54. U.S. Preventive Services Task Force: Screening for breast cancer, recommendation statement [accessed 2013 Nov. 10]. Available from: http://www.uspreventiveservicestaskforce.org/uspstf09/breastcancer/brcanrs.htm.
55. Indian Health Service 2009 National Summary Government Performance & Results Act [cited 2014 Jan 3]. Available from: http://www.ihs.gov/california/assets/File/GPRA/2009_National_Summary_FINAL.pdf.

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