Histopathological Predictors of Breast Cancer Death among Caucasians and Japanese in Hawaii[1]

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Abstract

In the United States, Caucasian women are at higher risk of death from breast cancer than age-matched Japanese-Americans. The tumors of Japanese-Americans exhibit a greater uniformity of nuclear grade (NG), greater degrees of intratumoral lymphocytic infiltration (LI), and more conspicuous sinus histiocytosis (SH) in the regional lymph nodes. To assess the impact of histopathology upon the ethnic disparity in breast cancer mortality, we compared the survival experience of Japanese and Caucasian women with breast cancer in Hawaii. The study group consisted of 443 women, aged 45–74, whose cancers were diagnosed between 1975 and 1980. Survival status at 9 or more years after diagnosis, known for 416 of these women, was used in the analyses. Age and tumor stage at diagnosis were significant predictors of breast cancer death in the logistic regression analysis. When histopathological predictor variables (NG, LI, and SH) were included in the model, age, stage, NG, and LI were independently predictive. Although NG predicted stage among all patients, and SH predicted stage among the women with invasive disease, race was an independent predictor breast cancer stage in multivariate analyses. Finally, analysis within stage subgroups revealed that race was independently predictive of cancer death among women with localized disease (confined to the breast) but not among women with regional spread (local extension or axillary nodes involves). These results indicate that histopathological differences contribute to, but only partially explain, the disparity in breast cancer mortality between Caucasians and Japanese in Hawaii.

Introduction

National Cancer Institute Surveillance, Epidemiology, and End Results Program data indicate that Caucasians are 1.6 times more likely to develop breast cancer than Japanese-Americans (1). The difference in breast cancer mortality is even more striking, with Caucasians having a 2.7-fold higher risk, due to a higher breast cancer survival rate among the Japanese (1, 2). In Hawaii, breast cancer in the Japanese is more likely to be diagnosed at an earlier stage than it is among age-matched Caucasians (3), and HTR[3] data have indicated that the racial disparity in breast cancer survival disappears after adjustment for disease stage (4, 5). Although these observations suggest that the survival advantage of the Japanese may be fully attributable to an earlier stage of breast cancer at diagnosis, the data do not exclude a contribution of additional prognostic factors. Moreover, the behavioral and biological bases of the race difference in breast cancer stage at presentation remain unexplained.

Differences in histopathological features between the breast cancers of Caucasians *versus* Japanese suggest possible biological differences between the racial groups (6–9). In international comparisons, the Japanese were more likely to have smaller tumors with less lymphatic channel invasion and fewer nodal metastases (6–8). Research in Hawaii has indicated that Japanese who develop breast cancer were more likely to have *in situ* tumors and tumors of a more uniform NG than age-matched Caucasians (9). The Japanese thus appear to develop breast tumors of lesser histological aggressiveness. In addition, racial differences in host response to breast cancer are suggested by observations that Japanese breast tumors exhibited greater degrees of intratumoral LI (6–11) and more conspicuous SH within regional lymph nodes (9, 12). Since NG, LI, and SH have been reported to influence breast cancer prognosis (13–15), the observed histopathological differences may contribute to the disparity in outcome between the Japanese and Caucasians.

The present study explores the hypothesis that biological factors contribute to the Japanese-Caucasian race disparity in breast cancer. The impact of histopathology upon breast cancer outcome was assessed by multivariate analyses of the survival status of Japanese and Caucasian breast cancer patients in Hawaii.

Materials and Methods

Study Population. This is a follow-up report of a study that compared the anatomic features of sequentially accessioned breast cancers in Caucasian and Japanese women living in Hawaii (9). Between the years 1975 and 1980, a total of 443 Japanese and Caucasian women,

Received 7/28/92.
[1] Supported in part by NIH Grant 1-NO1-CA15655 and Contract NO1-CB53884. Presented in part at the 28th Annual Meeting of the American Society of Clinical Oncology (abstract 55), May 17–19, 1992, San Diego, CA.
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[3] The abbreviations used are: HTR, Hawaii Tumor Registry; NG, nuclear grade; LI, lymphocytic infiltration; SH, sinus histiocytosis; LR, logistic regression.

aged 45–74, were diagnosed with breast cancer at one of seven civilian hospitals in Hawaii. They accounted for 92% of the newly diagnosed cases of breast cancer on Oahu. The case series consisted of 416 of these women for whom histopathology and survival status were known. The follow-up data were collected through the HTR, which is part of the Surveillance, Epidemiology, and End Results Program funded by the National Cancer Institute.

Dependent Variables. The primary dependent variable in this study was death due to breast cancer. Survival status was determined from the annual follow-up information collected by the HTR as of December 31, 1989 (cause of death assigned according to Surveillance, Epidemiology, and End Results Program criteria). Deaths due to causes other than breast cancer were considered nonevents and were grouped with alive.

A second dependent variable was stage of disease upon diagnosis. Stage was categorized as *in situ*, localized (*i.e.*, confined to the breast), regional (*i.e.*, by direct extension and/or lymph nodal involvement), and metastatic. The stage was coded from 1 to 4, representing the least to most invasive.

Independent Variables. Age, race, stage, and histopathological variables were used as independent variables. Age at diagnosis was categorized into 10-year age groups of 45–54, 55–64, and 65–74. A dummy variable was created for race, with Japanese as the reference group. Stage was categorized as described above. The analysis was confined to those anatomical factors that had demonstrated statistically significant differences among the Japanese and Caucasian breast cancer patients in the original report (9): NG, coded from least to most uniform on a 3-point scale; LI, coded from none to extensive on a 4-point scale; and SH, coded from grade 0 to 3. Tumor size and the nature of the tumor margins (rough or smooth) were part of the original study, but these variables were omitted from this study because they showed no interethnic differences. All histopathological variables were determined by consensus of 4 study pathologists who independently reviewed representative histological slides from each case. Although two-step surgical procedures (*i.e.*, biopsy, followed later by nodal dissection) may interfere with the interpretation of SH, one-step procedures (*i.e.*, biopsy, followed by immediate nodal dissection) were performed for the majority of breast cancer cases in Hawaii during the study period. For a full description of the histopathological analysis see Stemmermann *et al.* (9).

Statistical Analysis. χ^2 tests were performed to evaluate the association of each independent variable alone with death by breast cancer. Then, multivariate procedures were utilized to assess the combined effects of the independent variables. LR was used to model the binary outcome of death by breast cancer, and ordinary least squares was used to predict stage of breast cancer at diagnosis.

An LR model with age, race, and stage was performed to assess the impact of race on death by breast cancer while controlling for age and stage of disease. A second LR model was then fit which added NG, LI, and SH. NG, LI, and SH were recoded into binary variables for this LR analysis. NG was recoded as 0 for "most uniform" and 1 for "low-intermediate," LI was recoded as 0 for "extensive" and 1 for "none-moderate," and SH was recoded as 0 for "grade 3" and 1 for "grade 0–2." This model was repeated for patients with localized disease and those with regional disease, but not for patients with *in situ* or metastatic disease, due to the small number of cases in the latter subgroups.

To address the impact of race on stage of disease at presentation, ordinary least squares analyses were performed to predict breast cancer stage at presentation by age, race, NG, LI, and SH. The histological variables were entered as continuous variables. Analyses were conducted on all patients and on patients with invasive cancers only.

Table 1 Subject characteristics by breast cancer survival

	Total sample[a] (%)	Breast cancer deaths (%)
Total	416 (100.0)	134 (32.2)
Age at diagnosis[b]		
45–54	150 (36.1)	33 (22.0)
55–64	154 (37.0)	45 (29.2)
65–74	112 (26.9)	56 (50.0)
Race[b]		
Caucasian	201 (48.3)	84 (41.8)
Japanese	215 (51.7)	50 (23.3)
Stage[b]		
In situ	34 (8.2)	2 (5.9)
Localized	241 (58.3)	53 (22.0)
Regional	126 (30.5)	65 (51.6)
Metastatic	12 (2.9)	11 (91.7)
NG[b]		
Most uniform	66 (16.8)	7 (10.6)
Intermediate uniformity	305 (77.6)	108 (35.4)
Least uniform	22 (5.6)	12 (54.6)
LI		
Extensive	23 (6.0)	2 (8.7)
Moderate	95 (24.6)	33 (34.7)
Sparse	264 (68.4)	90 (34.1)
None	4 (1.0)	1 (25.0)
SH		
Grade 3	75 (22.3)	14 (18.7)
Grade 2	231 (68.8)	69 (29.9)
Grade 1	25 (7.4)	9 (36.0)
Grade 0	5 (1.5)	2 (40.0)

[a] Sum does not always equal 416 due to missing values.
[b] $P < 0.0001$, testing association of variable and breast cancer death by χ^2 test.

Results

The percentage of breast cancer deaths by age, race, stage, and extent of NG, LI, and SH are presented in Table 1. Among 215 Japanese and 201 Caucasian women with breast cancer, 134 (32%) had died of breast cancer. Older age, Caucasian race, more advanced stage at presentation, and less uniform NG were significantly associated with breast cancer death ($P < 0.0001$).

LI was not a significant predictor of breast cancer death in the univariate analysis; however, patients with "extensive" LI appeared to suffer substantially fewer breast cancer deaths (9%) than patients with LI of lesser degrees (34% deaths). This difference was significant when LI was collapsed into these two categories ($P < 0.05$). Similarly, grade 3 SH was associated with fewer breast cancer deaths than SH of grade 0–2 (18.7 *versus*

Table 2 Logistic regression models predicting death due to breast cancer

	Model 1 (n = 413)		Model 2 (n = 328)	
	Odds ratio	95% CI[a]	Odds ratio	95% CI[a]
Age				
45–54	1.00		1.00	
55–64	1.25	(0.70–2.22)	1.08	(0.56–2.06)
65–74	3.48	(1.92–6.30)	3.19	(1.60–6.34)
Race				
Caucasian	1.00		1.00	
Japanese	0.62	(0.39–1.00)	0.61	(0.35–1.05)
Stage				
Localized	1.00		1.00	
Regional	3.87	(2.37–6.31)	3.65	(2.08–6.40)
Metastatic	38.45	(4.71–314)	6.76	(0.58–79.2)
In situ	0.25	0.06–1.08)	0.49	(0.06–4.22)
NG				
Low-intermediate			1.00	
Most uniform			0.36	(0.13–0.97)
LI				
None-moderate			1.00	
Extensive			0.17	(0.03–0.81)
SH				
Grades 0–2			1.00	
Grade 3			0.76	(0.37–1.54)

[a] Ninety-five % confidence intervals.

Table 3 Multiple regression results predicting breast cancer stage at diagnosis

	All patients (n = 327)		Invasive cancers[a] (n = 312)	
	β	P	β	P
Constant	2.040	<0.0001	1.973	<0.0001
Age	−0.002	0.5	−0.004	0.3
Race (0 = Caucasian, 1 = Japanese)	−0.176	0.004	−0.152	0.007
NG (3-point scale)	−0.294	<0.0001	−0.104	0.1
LI (4-point scale)	0.045	0.4	0.033	0.5
SH (4-point scale)	−0.066	0.2	−0.146	0.003

[a] Excludes *in situ* stage.

30.7%; $P < 0.05$). Therefore, these binary histopathological variables were utilized in the subsequent LR models.

Table 2 summarizes results of the logistic models predicting breast cancer death. Controlling for age and stage (Model 1), the predictive value of race was only marginally significant, with the Japanese dying less frequently of breast cancer than the Caucasians (odds ratio = 0.62; $P = 0.05$). When histopathology was included in the analysis (Model 2), NG and LI were found to be predictive of breast cancer death independently of age, race, and stage. Patients with "most uniform" NG suffered significantly fewer breast cancer deaths than patients with "low-intermediate" NG (odds ratio = 0.36), and patients with "extensive" LI were less likely to die of their breast cancers than patients with "none-moderate" LI (odds ratio = 0.17). Older age and more advanced disease stage were significant adverse factors in both models.

To assess the effects of age, race, and histopathology upon breast cancer stage at diagnosis, multiple regression analyses were performed (Table 3). Among all patients, NG related inversely to tumor stage ($P < 0.0001$). Since highly uniform NG has been previously noted to significantly correlate with Japanese race and *in situ* stage (9), the analysis was repeated for women with invasive cancers only (excluding *in situ* stage). NG was no longer predictive in this latter model ($P = 0.1$), and SH gained inverse predictive significance ($P = 0.003$); *i.e.*, advanced disease stage was associated with lesser degrees of lymph node reaction. Although LI did not predict stage in either model, greater degrees of LI correlated with lesser uniformity of NG ($r = -0.22$; $P < 0.01$), whereas no other correlations were identified between the histopathological variables. In both models, race independently predicted stage: the Japanese presented with lower stage than the Caucasians.

To examine further the interactive effect of age, race, histopathology, and stage, multivariate analyses were performed predicting breast cancer death within stage groups, and the results with localized and regional stages are presented in Table 4. Age and race were significant predictors of survival status among women with localized but not regional stage. With localized stage, the oldest women (ages 65–74) were more likely to die of breast cancer than the youngest women (odds ratio = 4.57), and the Japanese were less likely than the Caucasians to succumb to their cancer (odds ratio = 0.36). Histopathology did not have prognostic significance within stage groups.

Discussion

Stemmermann *et al.* (9) have previously reported an analysis of pathologic findings among the study group. Although the Japanese and Caucasian breast tumors were of comparable mean sizes, significant histological differences were noted. Japanese cases had a significantly greater frequency of *in situ* cancer, uniform NG, moderate to extensive LI, and grade 3 SH in nonmetastatic lymph nodes. These findings are consistent with the favorable prognosis associated with these histopathological characteristics (13–15) and suggest that the ethnic disparities may be explained by biological differences in host response. To confirm the hypothesized prognostic relationships between ethnicity and histopathology, 9-year breast cancer survival status was obtained from the HTR, and multivariate statistical analyses were performed. The results support a conclusion that tumor and host biological characteristics are determinants of stage and survival among the Japanese and Caucasians of Hawaii.

As expected, age and stage at diagnosis were highly significant predictors of breast cancer death. The youngest women (aged 45–54) experienced the fewest deaths (22%), whereas women in the oldest age group (aged 65–74) experienced the highest breast cancer mortality (50%). The age-specific survival difference is consistent with reported data from Scandinavian cancer registries (16, 17) and is not explainable by a disproportionate number of women with advanced stage among the elderly, since the stage distributions within age groups were nearly identical. Furthermore, age retained prognostic significance even with stage included in the multivariate model, indicating an independent effect.

Table 4 Logistic regression analysis of the interactive effect of age, race, histopathology, and stage on breast cancer deaths

	Localized (n = 209)		Regional (n = 101)	
	Odds ratio	95% CI[a]	Odds ratio	95% CI[a]
Age				
45–54	1.00		1.00	
55–64	0.88	(0.32–2.39)	1.12	(0.44–2.87)
65–74	4.57	(1.81–11.5)	1.41	(0.48–4.15)
Race				
Caucasian	1.00		1.00	
Japanese	0.36	(0.17–0.79)	1.10	(0.48–2.56)
NG				
Low-intermediate	1.00		1.00	
Most uniform	0.30	(0.08–1.11)	0.58	(0.09–3.85)
LI				
None-moderate	1.00		1.00	
Extensive	0.39	(0.04–3.45)	0.13	(0.01–1.08)
SH				
Grades 0–2	1.00		1.00	
Grade 3	1.12	(0.43–2.94)	0.64	(0.20–1.96)

[a] Ninety-five % confidence intervals.

As reported in other studies (1, 2, 5), race was significantly associated with breast cancer death in the univariate model. However, in the multivariate models which controlled for age and stage (Table 2), the predictive significance of race was diminished, which is consistent with previously reported analyses of HTR data (4, 5). By contrast, histopathology was found to be significantly predictive of breast cancer death in univariate as well as in multivariate analyses. Highly uniform NG or extensive LI appeared to confer a favorable prognosis and appeared to supersede the effects of race, age, and even disease stage.

The present results are consistent with previous analyses of HTR data with respect to breast cancer stage presentation (3, 5), with the Japanese more likely to be diagnosed at an earlier stage than Caucasians. This race effect was independent of age at diagnosis and of histopathology, suggesting a contribution of other race-associated factors in determining the clinical presentation of breast cancer. Controlling for race, histopathology also independently predicted stage. Uniformity of NG was a characteristic feature of *in situ* tumors, suggesting that biological characteristics of the malignant cells are a principal determinant of invasiveness. The association between lower-grade SH and advanced invasive stage suggests that a systemic host response may be critical in controlling metastases to the regional nodes and beyond. Interestingly, although LI was a significant predictor of breast cancer survival, LI was not predictive of disease stage.

Consistent with the observations of LeMarchand *et al.* (5), the survival advantage of the Japanese over the Caucasians was diminished when controlling for stage, an effect attributable to the earlier stage at diagnosis among the Japanese. However, in an analysis of stage subgroups, race again emerged as a highly significant prognostic factor among women with localized breast cancer (*i.e.*, without chest wall invasion or nodal involvement). The Japanese with localized disease were only one-third as likely to die of their cancer than the Caucasians. Moreover, the predictive value of race was independent of age and histopathology. The survival disparity is not attributable to smaller tumors among the Japanese, since the Japanese and Caucasian breast tumors were of comparable sizes (9). These results point toward other race-related factors, as yet unidentified, which are important determinants of prognosis in node-negative breast cancer.

Possible mechanisms underlying the racial differences in breast cancer include (*a*) genetic (biological) factors and (*b*) psychosocial (cultural) and sociodemographic factors. The contribution of histopathology to breast cancer outcome among Caucasians and Japanese in Hawaii supports a role for biological factors in the race disparity. However, the histopathology does not fully account for the difference in breast cancer stage at diagnosis or for the outcome disparity in early-stage disease. Cultural and sociodemographic factors which result in differing behavioral risk factor profiles (e.g., dietary practices) or disparate utilization of health care services (e.g., delay in diagnosis, treatment compliance, etc.) are likely to play an additional contributory role in the breast cancer race disparity. Future studies of the interaction between behavior and biology may yield fresh leads toward delineating the determinants of breast cancer risk and outcome.

Acknowledgments

The authors gratefully acknowledge the contribution of many physicians on Oahu, and the cooperation of the following hospitals: Castle Memorial Hospital; Kaiser Medical Center; Kuakini Medical Center; Queen's Medical Center; St. Francis Hospital; Straub Clinic and Hospital; and Wahiawa General Hospital. We thank Lynne Wilkens for reviewing the manuscript and for her advice on the statistical analyses.

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Cancer Epidemiol Biomarkers Prev 1993;2:201-205.