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**13. ABSTRACT** *(Maximum 200 words)* We assessed distributions of breast cancer tumor characteristics and molecular prognostic biomarkers by race/ethnicity and socioeconomic position among paraffin-embedded tumor biopsy specimens from 135 US women (48 white, 44 black, 43 Asian) diagnosed with breast cancer between 1966 and 1990. No racial/ethnic or socioeconomic differences in distributions were observed for tumor stage, lymph node involvement, estrogen, progesterone, and epidermal growth factor receptors, oncogenes Her2/neu and p53, cytoplasmic proteins cathepsin-D and ps2, and two indices of cell growth, Ki67 and DNA ploidy, adjusting for age at diagnosis, menopausal status, place of birth, and, for racial/ethnic comparisons, socioeconomic position. Black and Asian women, however, were 3.5 times (95% confidence interval [CI] = 1.2-10.1) and 3.7 times (95% CI = 1.3-10.6) more likely than white women to have a tumor size of more than 20 mm, and Asian women were 3.4 times (95% CI = 1.1-10.4) more likely than black women to be positive for androgen receptor, adjusting for these same factors. No differences in distributions by socioeconomic position were observed for these latter two tumor characteristics. These data suggest that racial/ethnic and socioeconomic disparities in breast cancer survival are unlikely to be explained by differential distributions of ~~molecular breast cancer prognostic biomarkers.~~

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(Nancy Krieger) 6/3/98

PI - Signature Date

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## INTRODUCTION

Survival from breast cancer among women in the United States varies by race/ethnicity (1-15) and social class (10-18). As compared to non-Hispanic white women, survival rates are lower among black and American Indian women, higher among Japanese and Chinese women, and comparable among Hispanic women (all Hispanic women combined; breast cancer survival, however, is poorer among Puerto Rican as compared to non-Hispanic white women)(1-15). Survival rates are also inversely related to socioeconomic position, such that working class and poor women survive less long than professional and more affluent women (10-18). Suggesting a link between US racial/ethnic and socioeconomic patterns of breast cancer survival are racial/ethnic disparities in socioeconomic position: in addition to the poverty rate being two to three times higher among the black and Hispanic as compared to white population (19), total household wealth among white families is eight to ten times greater than among Hispanic and black families (20).

Reasons for racial/ethnic and socioeconomic inequalities in breast cancer survival remain unclear. Although late stage at diagnosis, linked to lack of access to medical care, may contribute to these disparities, US studies indicate that racial/ethnic and socioeconomic survival differences persist even after taking into account differential access to mammography and stage at diagnosis (3-5,12,16,21-23). Explaining inequalities in breast cancer survival may thus necessitate considering differences in tumor biologic characteristics potentially affecting tumor aggressiveness and responsiveness to treatment (4,6,7,24,25). These tumor biologic characteristics include: oncogenes such as her-2/neu, p53, and h-ras; cytoplasmic proteins ps2 and protease cathepsin-D; markers of cell growth, such as the Ki67 growth index and DNA ploidy; and receptors for estrogen, progesterone, androgen, and epidermal growth factor, whereby tumors positive for hormone receptors are associated with better prognosis (6,7,23-42).

Presently, little is known about distribution of breast cancer molecular prognostic biomarkers by race/ethnicity or socioeconomic position. Apart from studies on estrogen receptor status, most research on breast cancer molecular prognostic biomarkers has been based on samples of women who are chiefly or exclusively white or whose race/ethnicity has not been specified (26-42); the few comparing women from diverse racial/ethnic groups have not included socioeconomic data (6,7). Similarly, only two (24, 25) of the handful of studies examining US black/white differences in estrogen receptor status (7,23-25,43-50) have included measures of socioeconomic position, and they arrived at different conclusions about contributions of socioeconomic position to black/white differences in estrogen receptor status.

The purpose of our study accordingly was to compare distributions of breast cancer tumor characteristics and prognostic biomarkers by race/ethnicity and social class among US white, black and Asian women. Molecular prognostic biomarkers examined were: estrogen receptor, progesterone receptor, androgen receptor, epidermal growth factor receptor, Her2/neu, cathepsin-D, p53, ps2, Ki67, and DNA ploidy.

An additional goal of our study was to study to ascertain relationships of the selected biomarkers to survival, controlling for other biological and socioeconomic risk factors that affect survival. As explained in the body of

this report, however, the size of and number of deaths in our cohort turned out to be insufficient to permit valid analysis.

To summarize, the tasks required to conduct our study, as described in our initial proposal, were:

Task 1, Obtain medical charts and tumor blocks, Months 1-2:

a. Order medical charts; once receive them, abstract information on tumor characteristics and surgical accession number, make copy of pathology report
b. Using surgical accession number, order cases' tumor blocks from Central Repository

Task 2, Prepare blocks for delivery to laboratory, Months 3-4:

a. Once receive boxes of tumor blocks, sort through them to locate the desired blocks (and indicate position in boxes, so they can be returned to their original location)
b. Label blocks for analysis by laboratory; indicate case identification number and attach pathology report to blocks for each case

Task 3, Laboratory analysis for selected biomarkers, Months 5-14:

a. Establish data system for linking assay results to each cases' identification number and for keeping track of which blocks have been analyzed
b. Conduct immunohistochemical/image analysis for estrogen, progesterone, and epidermal growth factor receptors, cathepsin-D, her-2/neu, ps2, p53, h-ras, and ki67 (defined as positive or negative).
c. Enter assay results into ASCII file
d. Compile summary data of prevalence of the same biomarkers for paraffin-embedded specimens for breast cancer cases diagnosed in the early 1990s

Task 4, Mortality search, Months 13-14:

a. Determine vital status of each case, as of 12/31/94, using the MORTLINK file
b. Enter vital status of each case into ASCII file

Task 5, Assemble data base, Month 15:

a. Link assay data and vital status data to existing data file
b. Check new data set to ensure the data are accurate

Task 6, Data analysis, return blocks, Months 16-21:

a. Compare prevalence of biomarkers in the study's archival specimens to those of the recently-diagnosed cases
b. Conduct univariate and multivariate analyses comparing prevalence by race/ethnicity and socioeconomic position
c. Conduct Kaplan-Meier survival analysis and Cox regression analyses to evaluate the association of these biomarkers with survival among women in and across the three racial/ethnic groups, adjusting for other known biologic and socioeconomic risk factors for poor survival
d. Return blocks to Central Repository

Task 7, Prepare manuscript and talks based on study findings, Months 22-24

As of the date of preparing this final annual report (due June 30, 1998), we have fully completed Tasks 1 through 7.

**BODY**

*MATERIALS AND METHODS*

Study population

Our study was based on tumor specimens obtained from a random sample of 50 Asian, 50 black, and 50 white women selected for inclusion in a nested case-control study on relationships between exposure to organochlorines and risk of breast cancer (51). These women were members of a large health maintenance organization, the Kaiser Permanente Medical Program (KPMCP), who took a KPMCP multiphasic examination offered between 1964 and 1969 in the San Francisco Bay Area. Criteria for case inclusion were self-identified race/ethnicity and diagnosis with breast cancer at least six months after the multiphasic examination and prior to December 31, 1990. Among women selected, breast cancer was diagnosed between 1966 and 1990. Among the 50 Asian women, 52% were Chinese, 37% were Japanese, 3% were Filipino, 1% were Hawaiian, and 7% were of other or unknown Asian ethnicity. None of the white or black women were of Hispanic origin.

Data on the women's sociodemographic, reproductive, and anthropometric characteristics at the time of their multiphasic examination were obtained from the multiphasic exam (self-administered questionnaire supplemented by a physical examination which included measuring weight and height, with body mass index calculated as $kg/m^2$). To supplement data on educational level, the socioeconomic indicator available from the multiphasic exam, additional socioeconomic indicators characterized social class composition and poverty level for each woman's census block-group at her time of diagnosis, using measures validated in prior studies (52-53).

Data on age, parity, and menopausal status at diagnosis, tumor characteristics (stage, grade, laterality, size, lymph node involvement), and surgical accession number for each case's tumor block were obtained from medical chart review. Tumor stage was categorized as local, regional, and distant. Tumor size was dichotomized as $<20$ mm versus $\geq 20$ mm.

We were able to locate tumor blocks (archival paraffin-embedded tumor biopsy specimens) for 135 (90%) of the 150 study subjects (48 white women, 44 black women, 43 Asian women). The number of blocks per study subject ranged from 1 to 25. Tumor blocks were missing for 11 women and were unavailable for 4 women, either because no biopsy was performed (2 women) or the biopsy was not performed at KPMCP (2 women). Women missing and not missing tumor blocks did not vary with respect to race/ethnicity, socioeconomic position, age at diagnosis, and stage at diagnosis.

Biomarker assays

Pathology reports were reviewed to determine which block(s) should be analyzed for tumor markers. The block of choice was listed on the pathology report and the histotechnician was instructed to cut 12 thin sections from each

case. One H&E slide was prepared from each group and viewed under the microscope to assure the block contained tumor and that the tumor type and description were consistent with the pathology report. If so, the remaining slides were analyzed for the study's selected prognostic biomarkers. Analyses were conducted blind to the women's sociodemographic, anthropometric, and reproductive characteristics.

Biomarkers were determined by immunohistochemistry on thin sections (4-5 microns) prepared from paraffin blocks. Thin sections were attached to Probe-on Plus™ glass slides (Fisher, 15-187M), dried, and dewaxed through Hemo-De (Fisher, 15-182-507A), and rehydrated in ethanol (100, 95, 70%) followed by a 0.1% triton-phosphate buffered saline (TPBS) buffer. Sections for determination of estrogen, progesterone, and androgen receptor, Her2/neu, cathepsin-D, and p53 were then boiled in 0.1 N citric acid, pH 6.0, for 30 minutes for antigen retrieval. Sections for epidermal growth factor receptor determination were incubated with 0.1% Nargase in phosphate buffered saline (PBS) for 10 minutes, washed in TPBS, then blocked with 3% hydrogen peroxide in water, followed by a TPBS wash. Prepared sections were then incubated overnight with primary antibodies (estrogen receptor, AMAC, Inc.; progesterone receptor, Cell Analysis Systems Labs; androgen receptor and ps2, Biogenix; epidermal growth factor receptor and cathepsin-D, Triton Diagnostics; Her2/neu-AB3 and p53, Oncogene Science; Ki67, Immunotech) in 1% bovine serum albumin in PBS. Tissues were then washed with TPBS, incubated with biotinylated goad anti-mouse IgG (Zymed, 62-6540), followed by horseradish peroxidase streptavidin (Vector, SA-5004). Antigen was then revealed by incubating with the red substrate Aminoethyl carbazole (AEC, Zymed 00-2007). A cut-point of ≥10% tumor cells stained was used to categorize positive results for estrogen, progesterone, androgen, and epidermal growth factor receptor and also for Her2/neu, cathepsin-D, ps2, and Ki67; the respective cut-point for p53 was ≥5% and for S phase was ≥8% tumor cells stained.

Statistical analysis

We assessed distributions of sociodemographic, reproductive, anthropometric, and tumor characteristics of the breast cancer cases, overall and by race/ethnicity. Univariate analyses, including odds ratios and their 95% confidence intervals (CI), were performed to compare distributions of these characteristics by race/ethnicity and socioeconomic position, and to assess for potential confounders or effect modifiers (54) of distribution of tumor characteristics by race/ethnicity. We restricted measures of socioeconomic position to individual-level education and census block-group working class composition, since too few white and Asian women lived in impoverished block-groups to permit meaningful comparisons (Table 1). Relevant confounders identified were place of birth, and age at diagnosis. Multivariate logistic regression models (54-55), adjusting for these confounders, compared racial/ethnic and socioeconomic distributions of tumor stage, size, lymph node involvement and presence of molecular prognostic biomarkers. All analyses were performed with SAS version 6.0 (56).

*RESULTS*

Table 1 (see Appendix for all tables) presents sociodemographic, anthropometric, and reproductive characteristics, overall and by

race/ethnicity, of the 135 women included in this study. Asian women were youngest at diagnosis, least likely to have ever been pregnant, and most likely to have a low body mass index. White women were most likely to have been born outside of the US and to have completed four or more years of college education, and were least likely to live in working class or impoverished block-groups. All women had comparable health care coverage, since all belonged to the same health maintenance organization.

Overall, nearly 66% of women were diagnosed with local disease, 40% had tumors <20 mm, and 44% had lymph node involvement (Table 2). Tumor stage and lymph node involvement were comparable across racial/ethnic groups (Tables 2 and 4) and socioeconomic groups (Tables 3 and 5). Tumor size, however, was greater among black and Asian women, who were 3.5 times (95% confidence interval [CI] = 1.2, 10.1) and 3.7 times (95% CI = 1.3, 10.6), respectively, more likely than white women to have breast tumors ≥20 mm in size, adjusting for age at diagnosis, menopausal status, place of birth, and census block-group working class composition (Table 4). By contrast, tumor size did not notably differ by block-group working class composition and only tended to be larger among women who had not completed four or more years of college, adjusting for race/ethnicity, age at diagnosis, menopausal status, and place of birth (Tables 3 and 5).

With one exception, no racial/ethnic differences were apparent in distribution of tumor prognostic biomarkers, adjusting for relevant confounders (Tables 2 and 4). Asian women, though, were 3.4 times (95% CI = 1.1, 10.4) more likely than black women and tended to be 1.8 times (95% CI = 0.6, 5.2) more likely than white women to be positive for androgen receptor (Table 4). Combining women in all three racial/ethnic groups, approximately 70% of tumors were estrogen receptor positive and androgen receptor positive; slightly over half were positive for progesterone receptor, cathepsin D, and Ki67; slightly under 40% were positive for DNA ploidy; about 28% were positive for Her2/neu and for p53; slightly over 20% were positive for ps2; and 13% were positive for epidermal growth factor receptor. No racial/ethnic differences were observed for distributions of tumors that were both estrogen and progesterone receptor negative (age-adjusted odds ratio for black as compared to white women = 1.6 (95% CI = 0.5, 4.6), and for Asian as compared to white women = 0.9 (95% CI = 0.3, 2.9)).

No clear patterns of socioeconomic differences were apparent for distribution of breast cancer molecular prognostic biomarkers, adjusted for relevant confounders (Table 5). Estrogen and androgen receptor positive tumors, however, tended to be less common among women with less than four years of college education versus women with at least four years of college education, and tumors positive for p53 tended to be more frequent among the less educated women (Table 5).

*DISCUSSION*

Our study finds little evidence of racial/ethnic and socioeconomic differences in distribution of breast cancer molecular prognostic biomarkers among a sample of 135 white, black, and Asian women belonging to a large health maintenance organization in the San Francisco Bay Area. Taking into account potential confounders, however, tumor size varied by race/ethnicity, with size greater among black and Asian as compared to white women. These data

suggest that racial/ethnic and socioeconomic disparities in breast cancer survival are unlikely to be explained by distributions of breast cancer molecular prognostic biomarkers.

Interpretation of our results is limited by small sample size, often yielding large confidence intervals. Although confidence intervals for some of the elevated or reduced odds ratios might have excluded 1 were the sample size larger, absence of any clear racial/ethnic or socioeconomic pattern in size and direction of estimates is notable. Moreover, given the many comparisons performed, the observed greater prevalence of androgen receptor positive tumors among Asian as compared to black women might be due to chance.

Other factors affecting interpretation pertain to misclassification and bias concerning race/ethnicity, socioeconomic position, and prognostic biomarkers. Misclassification of race/ethnicity is likely to be small, since data were obtained by self-report. Selection bias related to socioeconomic position may affect generalizability of results, since findings may not be applicable to women without health care coverage. Even so, results should not be biased for women with health care coverage, since women included in this study were selected randomly from a cohort of women enrolled in a large health maintenance organization. Further suggesting minimal bias introduced by the study populations' socioeconomic profile, proportions of women in this study living in predominantly working class and poor block-groups were comparable to those for the general population in the San Francisco Bay Area in the 1980s (52). Use of census block-group measures of socioeconomic position, however, may have diluted estimates of effects of class position, as compared to measures based on individual-level social class data, and resulted in residual confounding affecting racial/ethnic comparisons adjusted for socioeconomic position (52,57). Even so, consistent or strong associations were not observed with available individual-level data on educational level. Lastly, although misclassification of prognostic biomarker status is possible, these data are unlikely to be biased by race/ethnicity or socioeconomic position, since assays were conducted blind to these case characteristics.

Comparison of our results to prior studies of race/ethnicity, socioeconomic position, and breast cancer prognostic biomarkers is complicated by measurement issues involving key study variables. First, epidemiologic analyses of breast cancer prognostic biomarkers employ a variety of assay techniques and also use different cut-points to denote positive results (7,23-50), rendering comparisons across studies difficult. Nevertheless, biomarker distributions observed in our study are highly consistent with reported positivity in other studies (7,23-50). Our results further provide additional evidence (58,59) that biomarkers from tumors preserved in paraffin blocks for up to 30 years were not compromised by degradation; one implication is that such tumor blocks may be a useful resource for cancer studies requiring data on tumor characteristics and extensive follow-up periods.

A second measurement issue concerns classification of race/ethnicity. Most other studies on race/ethnicity and breast cancer prognostic biomarkers do not state how they measured this key variable (6,24,43-50). One study, however, reported it classified race/ethnicity based on "appearance, patient questioning, surname, or medical record review" (7). Another stated it obtained data on race/ethnicity from a mixture of personal interviews and hospital records (25). Our study, by contrast, along with one other (23),

categorized race/ethnicity based on self-identification, as supported by current public health recommendations recognizing that race/ethnicity is a social, not biological, construct (60-63).

Despite potential differences in racial/ethnic classification, as well as regional differences in composition of racial/ethnic groups, several of our findings are consistent with those reported in prior studies. These include larger tumor size among African American as compared to white women (23) and no black/white differences in distributions of p53 (7,23), DNA ploidy (7,23), Her2/neu (7,23), Ki67 (23), epidermal growth factor receptor expression (23), progesterone receptor status (23), and estrogen receptor status (23,50). One investigation also reported no black/white differences for several tumor characteristics not assessed in our study: tumor differentiation, tumor grade, lipid-associated sialic acid, and carcinogenic embryonic antigen level (23).

In contrast to our results, however, several studies have reported that black women to be more likely than white women to have estrogen receptor negative tumors (7,24,25,44-49), and one found that black women were more likely than white women to have p53 gene alterations associated with poorer prognosis (6). An additional study also observed black women to be more likely than white women to have a rare allele of the protooncogene h-ras (not examined in our study), which was also associated with younger age at diagnosis, more aggressive tumors, and poorer survival (64).

Notably, only two of the studies reporting black/white differences in estrogen receptor status included socioeconomic variables in their analyses (24,25). Whereas one found that controlling for socioeconomic position accounted for black/white differences in estrogen receptor status (24), the other did not (25). Differences in results across these two studies and our own may in part result from divergent approaches to measuring and analyzing socioeconomic data.

The study that found socioeconomic position contributed to black/white differences in estrogen receptor status used census tract-based measures, with poverty areas defined as tracts where $\geq$7% of the population was below the poverty line, less educated areas as tracts where $\leq$67% of the adult population had completed 4 years of high school, and highly educated areas as tracts where >11% of the adult population had completed 4 or more years of college (24). Using these measures, this study found that black and white women residing in census tracts with, respectively, greater poverty and less education were more likely to have estrogen receptor negative tumors; contingently, adjusting for these socioeconomic measures greatly reduced black/white differences in estrogen receptor status.

By contrast, the other investigation obtained data on each woman's educational level, poverty index (ratio of annual family income to poverty level for a family of the same size, multiplied by 100), and occupation (25). Analyses of socioeconomic differences in estrogen receptor status were first conducted separately among black women and among white women and were restricted to comparisons of affluent (poverty index >400) to less affluent (poverty index $\leq$400) women. Notably, whereas 17% of black women and 54% of white women were classified as "affluent" by this measure, 42% of black women and 9% of white women had a poverty index of <126 (meaning they lived below or up to 126% of the poverty line). This study reported that lower socioeconomic

position was associated with lower prevalence of estrogen receptors only among breast tumors from white, but not black women, and thus, that adjusting for this socioeconomic measure did not notably alter the greater likelihood of black women to have estrogen receptor negative tumors (25). Lack of precision in evaluating socioeconomic position among the black women, along with limited overlap in distributions between the black and white women, may have contributed to these findings. Interestingly, however, a British study examining social class in relation to estrogen receptor status found no difference between poor and affluent white women, using the Carstairs index of deprivation, nor did it detect socioeconomic differences in tumor size, nodal status, or tumor grade (65).

Additional survival analyses

In additional analyses, we sought to ascertain the prognostic significance of the selected biomarkers among women in each racial/ethnic group, stratified by socioeconomic position. To accomplish this task, we ascertained each woman's vital status as of December 31, 1994, using the program MORTLINK, which is an updated and modified version of the CAMLIS system (66). We then used two different analytic approaches to evaluate relationships between the presence of the selected biomarkers and length of survival, adjusting for other biological and socioeconomic risk factors: Kaplan-Meier survival analyses and Cox proportional hazard regression analyses (54,67). We quickly ascertained, however, that we lacked sufficient number of deaths (events) to permit valid analysis.

First, among the total sample of 135 women, only 25 deaths occurred during the follow-up period. These were distributed as follows: among white women, 11 deaths among 48 cases; among the black women, 9 deaths among 44 cases; and among the Asian women, 5 deaths among 43 cases. The percent censored (meaning, did not die by end of follow-up) ranged from 77 to 88.4 percent. Based on preliminary Kaplan-Meier analyses, we determined that there were no differences in survival rates by race/ethnicity (logrank test p value = 0.23), nor were there differences by educational level (logrank test p value = 0.51, for all women combined) or the working class block-group measure of socioeconomic position (logrank test p-value = 0.45). When analyzed by Cox regression models, we obtained comparable results, with the 95% CI for the hazards ratio so large as to render dubious interpretation of the point estimate. For example, the hazard ratio for comparisons of black versus white survival overall was 0.84 (95% CI = 0.34, 1.87). Thus, while the point estimate of 0.8 may be reasonable, as compared to prior studies on black/white differences in breast cancer survival (1-8,1-15,21), our findings in fact have little meaning, on account of the large confidence interval. Given that many studies have consistently reported significant racial/ethnic and socioeconomic disparities in breast cancer survival (1-15), our study clearly had insufficient power to contribute meaningfully to this literature.

Our analyses of survival in relationship to estrogen receptor status are even more illustrative of problems imposed by small sample size. The distribution of deaths among estrogen receptor negative (ER-) and positive (ER+) cases was as follows:

ER-

white women: 6 deaths out of 12 cases
black women: 3 deaths out of 13 cases
Asian women: 2 deaths out of 12 cases

ER+

white women: 8 deaths out of 35 cases
black women: 6 deaths out of 29 cases
Asian women: 3 deaths out of 30 cases

When we tried to compare survival, of women with ER- versus ER+ tumors, the p-value for the logrank test, for women in all racial/ethnic groups combined, equaled 0.42, and differences were even less significant for analyses further stratified by race/ethnicity. Using Cox regression models, we found that the hazard ratio, comparing survival among ER- to ER+ women (all racial/ethnic groups combined) was 0.56 (95% CI = 0.26, 1.22). Given the well-documented value of estrogen receptor status in predicting breast cancer survival (7,23-25,28,43-50), it again is clear that the small number of women in our study, combined with the small number of deaths, renders moot meaningful interpretation of our survival analyses.

We encountered similar problems, reflecting small sample size and large confidence intervals, in our analyses of all the other prognostic biomarkers examined in our study. Thus, we do not plan to report any of our findings on breast cancer survival and instead encourage that larger studies be conducted in the future, with adequate sample size, to address the questions our study sought to answer about prognostic significance of breast cancer molecular prognostic biomarkers among women in diverse racial/ethnic groups, stratified by socioeconomic position.

**CONCLUSIONS**

Taking into account difficulties in measuring both race/ethnicity and socioeconomic position (60-63), our findings suggest that, despite marked differences in socioeconomic position, white, black, and Asian women have comparable distributions of breast cancer molecular prognostic biomarkers. Our study thus lends further support to the hypothesis that experiences associated with race/ethnicity and socioeconomic position, other than tumor biological properties, may contribute to racial/ethnic and socioeconomic disparities in breast cancer survival. Possible factors to consider include co-morbidity and poorer baseline health status, compromised immunologic systems (perhaps reflecting stress-induced changes stemming from racial discrimination and socioeconomic deprivation), and exposure to environmental and occupational agents affecting tumor development (25,65,68). As one step toward evaluating these hypotheses more definitively, future research should characterize distribution of prognostic biomarkers in larger populations of women diagnosed with breast cancer who are diverse in their racial/ethnic and socioeconomic composition, using well-defined and consistent measures of racial/ethnic self-identification, socioeconomic position, and molecular prognostic biomarkers.

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**APPENDIX 1**

Table 1. Selected sociodemographic, reproductive, and anthropometric variables of 135 women diagnosed with breast cancer, overall and by race/ethnicity, San Francisco Bay Area, 1966-1990

Table 2. Selected tumor characteristics and prognostic biomarkers of 135 women diagnosed with breast cancer, overall and by race/ethnicity, San Francisco Bay Area, 1966-1990.

Table 3. Odds ratios and 95% confidence intervals of tumor characteristics and prognostic biomarkers by socioeconomic position, 135 women diagnosed with breast cancer, San Francisco Bay Area, 1966-1990.

Table 4. Odds ratios and 95% confidence intervals of tumor characteristics and prognostic biomarkers by racial/ethnic group from logistic regression, adjusted for age at diagnosis, menopausal status, place of birth, and working class block-group composition, for 135 women diagnosed with breast cancer, San Francisco Bay Area, 1966-1990.

Table 5. Odds ratios and 95% confidence intervals of tumor characteristics and prognostic biomarkers by socioeconomic position from logistic regression, adjusted for race/ethnicity, age at diagnosis, menopausal status, and place of birth, for 135 women diagnosed with breast cancer, San Francisco Bay Area, 1966-1990.

**Table 1. Selected sociodemographic, reproductive, and anthropometric variables of 135 women diagnosed with breast cancer, overall and by race/ethnicity, San Francisco Bay Area, 1966-1990.**

| Characteristics | | Total (n=135) Frequency | (%) | White (n=48) Frequency | (%) | Black (n=44) Frequency | (%) | Asian (n=43) Frequency | (%) |
|---|---|---|---|---|---|---|---|---|---|
| Age at Diagnosis | < 55 years old | 48 | (35.6) | 14 | (29.2) | 14 | (31.8) | 20 | (46.5) |
| | ≥ 55 years old | 87 | (64.4) | 34 | (70.8) | 30 | (68.2) | 23 | (53.5) |
| Birth Place | US-Born | 102 | (81.5) | 34 | (73.9) | 36 | (90.0) | 31 | (81.6) |
| | Foreign | 23 | (18.5) | 12 | (26.1) | 4 | (10.0) | 7 | (18.4) |
| Working Class (WC) Block Group | ≥ 66% WC | 88 | (66.7) | 28 | (60.9) | 34 | (77.3) | 26 | (61.9) |
| | < 66% WC | 44 | (33.3) | 18 | (39.1) | 10 | (22.7) | 16 | (38.1) |
| Poverty Block Group | ≥ 20% Poor | 22 | (16.7) | 2 | (4.3) | 15 | (34.1) | 5 | (11.9) |
| | < 20% Poor | 110 | (83.3) | 44 | (95.7) | 29 | (65.9) | 37 | (88.1) |
| Level of Education | < 4 year-college | 106 | (79.1) | 32 | (68.1) | 37 | (84.1) | 37 | (86.0) |
| | ≥ 4 year-college | 28 | (20.9) | 15 | (31.9) | 7 | (15.9) | 6 | (14.0) |
| Pregnancy History | Ever Pregnant | 104 | (77.6) | 38 | (79.2) | 36 | (81.8) | 30 | (71.4) |
| | Never Pregnant | 30 | (22.4) | 10 | (20.8) | 8 | (18.2) | 12 | (28.6) |
| Age at Menopause | < 45 years | 23 | (17.8) | 4 | (8.7) | 17 | (41.5) | 2 | (4.8) |
| | 45-54 years | 66 | (51.2) | 28 | (60.9) | 13 | (31.7) | 25 | (59.5) |
| | ≥ 55 years | 12 | (9.3) | 5 | (10.9) | 5 | (12.2) | 2 | (4.8) |
| | Premenopausal | 28 | (21.7) | 9 | (19.5) | 6 | (14.6) | 13 | (31.0) |
| Body Mass Index | < 21 | 21 | (16.7) | 3 | (7.0) | 1 | (2.3) | 14 | (36.8) |
| | 21-24 | 51 | (40.5) | 20 | (46.5) | 13 | (31.0) | 18 | (47.4) |
| | ≥ 25 | 54 | (42.8) | 20 | (46.5) | 28 | (66.7) | 6 | (15.8) |

Note: a small number of women (usually <3%) were missing data for selected characteristics; percentages are based of those with complete data.

**Table 2. Selected tumor characteristics and prognostic biomarkers of 135 women diagnosed with breast cancer, overall and by race/ethnicity, San Francisco Bay Area, 1966-1990.**

| Characteristics | | Total (n=135) Frequency | (%) | White (n=48) Frequency | (%) | Black (n=44) Frequency | (%) | Asian (n=43) Frequency | (%) |
|---|---|---|---|---|---|---|---|---|---|
| Tumor Stage | Local | 88 | (65.7) | 29 | (61.7) | 28 | (63.6) | 31 | (72.1) |
| | Regional/Distant | 46 | (34.3) | 18 | (38.3) | 16 | (36.4) | 12 | (27.9) |
| Tumor Size | < 20mm | 50 | (40.0) | 24 | (58.5) | 14 | (33.3) | 12 | (28.6) |
| | 20-49mm | 55 | (44.0) | 14 | (34.2) | 18 | (42.9) | 23 | (54.8) |
| | ≥ 50mm | 20 | (16.0) | 3 | (7.3) | 10 | (23.8) | 7 | (16.6) |
| Lymph Node Involvement | Any | 59 | (43.7) | 24 | (50.0) | 19 | (44.2) | 16 | (37.2) |
| | None | 76 | (56.3) | 24 | (50.0) | 24 | (55.8) | 27 | (67.8) |
| Estrogen | ≥ 10% stained | 94 | (71.8) | 35 | (74.5) | 29 | (69.0) | 30 | (71.4) |
| Progesterone | ≥ 10% stained | 71 | (54.2) | 27 | (57.4) | 21 | (50.0) | 23 | (54.8) |
| Androgen | ≥ 10% stained | 90 | (69.2) | 34 | (72.3) | 24 | (58.5) | 32 | (76.2) |
| EGFR | ≥ 10% stained | 17 | (13.0) | 5 | (10.6) | 5 | (11.9) | 7 | (16.7) |
| Her2/Neu | ≥ 10% stained | 37 | (28.5) | 14 | (29.8) | 8 | (19.5) | 15 | (35.7) |
| Cathepsin D | ≥ 10% stained | 69 | (54.1) | 30 | (63.8) | 18 | (42.9) | 21 | (51.2) |
| P53 | ≥ 5% stained | 28 | (21.4) | 9 | (19.1) | 7 | (16.7) | 12 | (28.6) |
| Ps2 | ≥ 10% stained | 35 | (27.6) | 15 | (31.9) | 10 | (25.0) | 10 | (25.0) |
| Ki67 | ≥ 10% stained | 65 | (50.8) | 22 | (46.8) | 22 | (53.7) | 21 | (52.5) |
| DNA Ploidy | ≥ 8% stained | 45 | (38.5) | 16 | (37.2) | 13 | (34.2) | 16 | (44.4) |

Note: a small number of women (usually <3%) were missing data for selected characteristics; percentages are based on those with complete data.
EGRF = Epidermal Growth Factor Receptor

**Table 3. Odds ratios and 95% confidence intervals of tumor characteristics and prognostic biomarkers by socioeconomic position, 135 women diagnosed with breast cancer, San Francisco Bay Area, 1966-1990.**

| Characteristics | | Working Class (WC) Block Group ≥ 66% WC versus < 66% WC | | Education Level < 4 year-college versus ≥ 4 year-college | |
|---|---|---|---|---|---|
| | | OR | (95% CI) | OR | (95% CI) |
| Tumor Size | (≥ 20mm versus <20mm) | 0.94 | (0.44-2.00) | 3.33 | (1.40-7.93) |
| Lymph Node Involvement | (Any versus None) | 1.56 | (0.66-3.68) | 1.21 | (0.45-3.26) |
| Tumor Stage | (Reg./Dist. versus None) | 1.39 | (0.66-2.99) | 1.21 | (0.47-2.75) |
| Estrogen | (+ versus -) | 1.34 | (0.59-3.07) | 0.25 | (0.07-0.90) |
| Progesterone | (+ versus -) | 2.03 | (0.95-4.32) | 0.43 | (0.17-1.07) |
| Androgen | (+ versus -) | 0.54 | (0.25-1.19) | 0.34 | (0.11-1.06) |
| EGFR | (+ versus -) | 0.85 | (0.28-2.62) | 0.83 | (0.25-2.79) |
| Her2/Neu | (+ versus -) | 1.03 | (0.45-2.33) | 2.59 | (0.83-8.13) |
| Cathepsin D | (+ versus -) | 1.39 | (0.66-2.92) | 1.31 | (0.56-3.07) |
| P53 | (+ versus -) | 0.38 | (0.13-1.10) | 9.24 | (1.20-71.40) |
| Ps2 | (+ versus -) | 1.15 | (0.50-2.63) | 0.87 | (0.33-2.34) |
| Ki67 | (+ versus -) | 0.83 | (0.39-1.73) | 2.69 | (1.07-6.80) |
| DNA Ploidy | (+ versus -) | 1.73 | (0.79-3.77) | 2.72 | (0.93-7.94) |

**Table 4. Odds ratios and 95% confidence intervals of tumor characteristics and prognostic biomarkers by racial/ethnic group from logistic regression, adjusted for age at diagnosis, menopausal status, place of birth, and working class block-group composition, for 135 women diagnosed with breast cancer, San Francisco Bay Area, 1966-1990.**

| Characteristics | | Black versus White | | Asian versus Black | | Asian versus White | |
|---|---|---|---|---|---|---|---|
| | | OR | (95% CI) | OR | (95% CI) | OR | (95% CI) |
| Tumor Size | (≥ 20mm versus <20mm) | 3.53 | (1.23-10.11) | 1.05 | (0.37-2.98) | 3.72 | (1.31-10.56) |
| Lymph Node Involvement | (Any versus None) | 1.30 | (0.42-4.07) | 0.62 | (0.20-1.99) | 0.81 | (0.27-2.42) |
| Tumor Stage | (Reg./Dist. versus None) | 1.24 | (0.47-3.31) | 0.47 | (0.17-1.36) | 0.59 | (0.21-1.63) |
| Estrogen | (+ versus -) | 0.82 | (0.28-2.39) | 1.58 | (0.52-4.83) | 1.30 | (0.43-3.89) |
| Progesterone | (+ versus -) | 0.83 | (0.32-2.18) | 1.48 | (0.54-4.03) | 1.23 | (0.47-3.25) |
| Androgen | (+ versus -) | 0.52 | (0.19-1.43) | 3.38 | (1.10-10.37) | 1.75 | (0.60-5.15) |
| EGFR | (+ versus -) | 1.69 | (0.39-7.27) | 1.12 | (0.28-4.39) | 1.89 | (0.47-7.66) |
| Her2/Neu | (+ versus -) | 0.47 | (0.13-1.63) | 2.54 | (0.74-6.77) | 1.19 | (0.41-3.44) |
| Cathepsin D | (+ versus -) | 0.48 | (0.18-1.26) | 1.63 | (0.60-4.45) | 0.78 | (0.30-2.06) |
| P53 | (+ versus -) | 1.83 | (0.49-6.83) | 1.27 | (0.36-4.45) | 2.32 | (0.65-8.35) |
| Ps2 | (+ versus -) | 0.62 | (0.21-1.82) | 1.24 | (0.40-3.83) | 0.76 | (0.26-2.19) |
| Ki67 | (+ versus -) | 1.45 | (0.57-3.74) | 0.84 | (0.31-2.25) | 1.21 | (0.47-3.15) |
| DNA Ploidy | (+ versus -) | 1.22 | (0.41-3.61) | 1.22 | (0.43-3.51) | 1.00 | (0.33-3.00) |

**Table 5. Odds ratios and 95% confidence intervals of tumor characteristics and prognostic biomarkers by socioeconomic position from logistic regression, adjusted for race/ethnicity, age at diagnosis, menopausal status, and place of birth, for 135 women diagnosed with breast cancer, San Francisco Bay Area, 1966-1990.**

| Characteristics | | Working Class (WC) Block Group ≥ 66% WC versus < 66% WC | | Education Level < 4 year-college versus ≥ 4 year-college | |
|---|---|---|---|---|---|
| | | OR | (95% CI) | OR | (95% CI) |
| Tumor Size | (≥ 20mm versus <20mm) | 1.64 | (0.66-4.07) | 2.10 | (0.78-5.62) |
| Lymph Node Involvement | (Any versus None) | 2.06 | (0.77-5.52) | 1.16 | (0.39-3.41) |
| Tumor Stage | (Reg./Dist. versus None) | 1.82 | (0.77-4.34) | 1.15 | (0.44-3.04) |
| Estrogen | (+ versus -) | 1.40 | (0.53-3.73) | 0.29 | (0.08-1.11) |
| Progesterone | (+ versus -) | 1.65 | (0.70-3.90) | 0.57 | (0.21-1.52) |
| Androgen | (+ versus -) | 0.49 | (0.20-1.21) | 0.28 | (0.08-0.94) |
| EGFR | (+ versus -) | 0.73 | (0.20-2.62) | 0.62 | (0.17-2.30) |
| Her2/Neu | (+ versus -) | 0.68 | (0.25-1.87) | 1.97 | (0.57-6.77) |
| Cathepsin D | (+ versus -) | 1.23 | (0.52-2.95) | 1.46 | (0.55-3.86) |
| P53 | (+ versus -) | 0.39 | (0.11-1.45) | 7.45 | (0.90-61.97) |
| Ps2 | (+ versus -) | 1.17 | (0.46-2.96) | 1.09 | (0.36-3.28) |
| Ki67 | (+ versus -) | 0.90 | (0.39-2.09) | 2.38 | (0.85-6.65) |
| DNA Ploidy | (+ versus -) | 2.06 | (0.83-5.13) | 2.72 | (0.83-8.90) |

**APPENDIX #2**

See enclosed reprint of published paper (3 reprints enclosed):

Krieger N, Van Den Eeden SK, Zava D, Okamoto A. Race/ethnicity, social class, and prevalence of breast cancer molecular prognostic biomarkers: a study of white, black, and Asian women in the San Francisco Bay Area. Ethnicity & Disease 1997; 7:137-149.

**Bibliography of published papers and meeting abstracts**

Published paper:

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# RACE/ETHNICITY, SOCIAL CLASS, AND PREVALENCE OF BREAST CANCER PROGNOSTIC BIOMARKERS: A STUDY OF WHITE, BLACK, AND ASIAN WOMEN IN THE SAN FRANCISCO BAY AREA

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We assessed distributions of breast cancer prognostic biomarkers by race/ethnicity and socioeconomic position among paraffin-embedded tumor biopsy specimens from 135 US women (48 white women, 44 black women, 43 Asian women) diagnosed with breast cancer between 1966 and 1990. No racial/ethnic or socioeconomic differences in distributions were observed for tumor stage, lymph node involvement, estrogen, progesterone, and epidermal growth factor receptors, oncogenes such as Her2/neu and p53, cytoplasmic proteins cathepsin-D and ps2, and two indices of cell growth, Ki67 and DNA ploidy, adjusting for age at diagnosis, menopausal status, place of birth and, for racial/ethnic comparisons, working class composition of census block-group at diagnosis. Black and Asian women, however, were 3.5 times (95% confidence interval [CI] = 1.2, 10.1) and 3.7 times (95% CI = 1.3, 10.6), respectively more likely than white women to have a tumor size of ≥ 20 mm, and Asian women were 3.4 times (95% CI = 1.1, 10.4) more likely than black women to be positive for androgen receptor, adjusting for these same factors. No differences in distributions by socioeconomic position were observed for these latter two tumor characteristics. These data suggest that racial/ethnic and socioeconomic disparities in breast cancer survival are unlikely to be explained solely by differential distributions of molecular breast cancer prognostic biomarkers. (*Ethnicity Dis.* 1997;7:137-149)

KEY WORDS: Asian, Black, Breast Cancer, Prognostic Biomarkers, Race/ethnicity, Social Class, Socioeconomic Factors

Survival from breast cancer among women in the United States varies by race/ethnicity[1–15] and social class.[10–18] As compared to non-Hispanic white women, survival rates are lower among black and American Indian women, higher among Japanese and Chinese women, and comparable among Hispanic women (as a group; however, breast cancer survival is poorer among Puerto Rican as compared to non-Hispanic white women).[1–15] Survival rates are also inversely related to socioeconomic position, such that working class and poor women live fewer years than professional and more affluent women.[10–18] Racial/ethnic disparities in socioeconomic position suggest a link between U.S. racial/ethnic and socioeconomic patterns of breast cancer survival. In addition to the poverty rate being two to three times higher among the black and Hispanic as compared to the white population,[19] total household wealth among white families is eight to ten times greater than among Hispanic and black families.[20]

Reasons for racial/ethnic and socioeconomic inequalities in breast cancer survival remain unclear. Although late-stage diagnosis combined with lack of access to medical care may contribute to these disparities, U.S. studies indicate that racial/ethnic and socioeconomic survival differences persist

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even after taking into account differential access to mammography and stage at diagnosis.[3–5,12,16,21–23] It may therefore be necessary to consider differences in tumor biologic characteristics, which potentially affect tumor aggressiveness and responsiveness to treatment[4,6,7,24,25] when attempting to explain inequalities in breast cancer survival. These tumor biologic characteristics include: oncogenes such as Her2/neu, p53, and h-ras; cytoplasmic proteins ps2 and protease cathepsin-D; markers of cell growth, such as the Ki67 growth index and DNA ploidy; and receptors for estrogen, progesterone, androgen, and epidermal growth factor, whereby tumors positive for hormone receptors are associated with better prognosis.[6,7,23–42] Of these, p53 and androgen receptor most likely represent inherited genetic alterations, whereas the rest reflect acquired tumor characteristics.

Presently, little is known about the distribution of diverse breast cancer molecular prognostic biomarkers by race/ethnicity or socioeconomic position. Apart from studies on estrogen receptor status, most research on breast cancer prognostic biomarkers has been based on samples of women who are chiefly or exclusively white, or whose race/ethnicity has not been specified.[26–42] Moreover, the two investigations comparing women from diverse racial/ethnic groups have not included socioeconomic data.[6–7] Similarly, only two[24–25] of the handful of studies examining US black/white differences in estrogen receptor status[7,23–25,43–50] have included measures of socioeconomic position, and they arrived at different conclusions about contributions of socioeconomic position to black/white differences in estrogen receptor status.

The purpose of our study, accordingly, was to compare distributions of breast cancer tumor characteristics and prognostic biomarkers by race/ethnicity and social class among U.S. white, black and Asian women. Prognostic biomarkers examined were: estrogen receptor, progesterone receptor, androgen receptor, epidermal growth factor receptor, Her2/neu, cathepsin-D, p53, ps2, Ki67, and DNA ploidy.

## Methods

### *Study population*

Our study was based on tumor specimens obtained from a random sample of 50 Asian, 50 black, and 50 white women selected for inclusion in a nested case-control study on relationships between exposure to organochlorines and risk of breast cancer.[51] These women were members of a large health maintenance organization, the Kaiser Permanente Medical Program (KPMCP), who took a KPMCP multiphasic examination offered between 1964 and 1969 in the San Francisco Bay Area. Criteria for case inclusion were self-identified race/ethnicity and diagnosis with breast cancer at least six months after the multiphasic examination and prior to December 31, 1990. Among women selected, breast cancer was diagnosed between 1966 and 1990. Among the 50 Asian women, 52% were Chinese, 37% were Japanese, 3% were Filipino, 1% were Hawaiian, and 7% were of other or unknown Asian ethnicity. None of the white or black women were of Hispanic origin.

Data on the women's sociodemographic, reproductive, and anthropometric characteristics at the time of their multiphasic examination were obtained from the multiphasic exam (self-administered questionnaire supplemented by a physical examination which included measuring weight and height, with body mass index calculated as $kg/m^2$). To supplement data on educational level, the socioeconomic indicator available from the multiphasic exam, additional socioeconomic indicators characterized social class composition and poverty level for each woman's census block-group at her time of diagnosis, using measures validated in prior studies.[52–53]

Data on age, parity, and menopausal status at diagnosis, tumor characteristics

(stage, grade, laterality, size, lymph node involvement), and surgical accession number for each case's tumor block were obtained from medical chart review. Tumor stage was categorized as local, regional, and distant. Tumor size was dichotomized as <20 mm versus ≥ 20 mm.

We were able to locate tumor blocks (archival paraffin-embedded tumor biopsy specimens) for 135 (90%) of the 150 study subjects (48 white women, 44 black women, 43 Asian women). The number of blocks per study subject ranged from 1 to 25. Tumor blocks were missing for 11 women and were unavailable for 4 women, either because no biopsy was performed (2 women) or the biopsy was not performed at KPMCP (2 women). Whether the women had or did not have tumor blocks, they did not vary with respect to race/ethnicity, socioeconomic position, age at diagnosis, and stage at diagnosis.

### *Biomarker assays*

Pathology reports were reviewed to determine which block(s) should be analyzed for tumor markers. The block of choice was listed on the pathology report and the histotechnician was instructed to cut 12 thin sections from each case. One H&E slide was prepared from each group and viewed under the microscope to assure the block contained tumor, and that the tumor type and description were consistent with the pathology report. If so, the remaining slides were analyzed for the study's selected prognostic biomarkers. Analyses were conducted blind to the women's sociodemographic, anthropometric, and reproductive characteristics.

Biomarkers were determined by immunohistochemistry on thin sections (4–5 microns) prepared from paraffin blocks. Thin sections were attached to Probe-on Plus™ glass slides (Fisher, 15–187M), dried, and dewaxed through Hemo-De (Fisher, 15–182–507A), and rehydrated in ethanol (100, 95, 70%) followed by a 0.1% triton-phosphate buffered saline (TPBS) buffer. Sections for determination of estrogen, progesterone, and androgen receptor, Her2/neu, cathepsin-D, and p53 were then boiled in 0.1 N citric acid, pH 6.0, for 30 minutes for antigen retrieval. Sections for epidermal growth factor receptor determination were incubated with 0.1% Nargase in phosphate buffered saline (PBS) for 10 minutes, washed in TPBS, then blocked with 3% hydrogen peroxide in water, followed by a TPBS wash. Prepared sections were then incubated overnight with primary antibodies (estrogen receptor, AMAC, Inc.; progesterone receptor, Cell Analysis Systems Labs; androgen receptor and ps2, Biogenix; epidermal growth factor receptor and cathepsin-D, Triton Diagnostics; Her2/neu-AB3 and p53, Oncogene Science; Ki67, Immunotech) in 1% bovine serum albumin in PBS. Tissues were then washed with TPBS, incubated with biotinylated goad anti-mouse IgG (Zymed, 62–6540), followed by horseradish peroxidase streptavidin (Vector, SA-5004). Antigen was then revealed by incubating with the red substrate Aminoethyl carbazole (AEC, Zymed 00–2007). A cut-point of ≥10% tumor cells stained was used to categorize positive results for estrogen, progesterone, androgen, and epidermal growth factor receptor, as well as for Her2/neu, cathepsin-D, ps2, and Ki67; the respective cut-point for p53 was ≥5% and, for S phase, was ≥8% tumor cells stained.

### *Statistical analysis*

We assessed distributions of sociodemographic, reproductive, anthropometric, and tumor characteristics of the breast cancer cases, overall and by race/ethnicity. Univariate analyses, including odds ratios and their 95% confidence intervals (CI), were performed to compare distributions of these characteristics by race/ethnicity and socioeconomic position, and to assess for potential confounders or effect modifiers[54] of distribution of tumor characteristics by race/

ethnicity. We restricted measures of socioeconomic position to individual-level education and census block-group working class composition, since too few white and Asian women lived in impoverished block-groups to permit meaningful comparisons (Table 1). Relevant confounders identified were place of birth, menopausal status, and age at diagnosis. Multivariate logistic regression models,[54-55] adjusting for these confounders, compared racial/ethnic and socioeconomic distributions of tumor stage, size, lymph node involvement and presence of prognostic biomarkers. All analyses were performed with SAS version 6.0.[56]

## Results

Table 1 presents sociodemographic, anthropometric, and reproductive characteristics, overall and by race/ethnicity, of the 135 women included in this study. Asian women were youngest at diagnosis, least likely to have ever been pregnant, and most likely to have a low body mass index. White women were most likely to have been born outside the US and to have completed four or more years of college education, and were least likely to live in working class or impoverished block-groups. All women had comparable health care coverage, since all belonged to the same health maintenance organization.

Overall, nearly 66% of women were diagnosed with local disease, 40% had tumors <20 mm, and 44% had lymph node involvement (Table 2). Tumor stage and lymph node involvement were comparable across racial/ethnic groups (Tables 2 and 4) and socioeconomic groups (Tables 3 and 5). Tumor size, however, was greater among black and Asian women, who were 3.5 times (95% confidence interval [CI] = 1.2, 10.1) and 3.7 times (95% CI = 1.3, 10.6), respectively, more likely than white women to have breast tumors ≥20 mm in size, adjusting for age at diagnosis, menopausal status, place of birth, and census block-group working class composition (Table 4). By contrast, tumor size did not notably differ by block-group working class composition, and only tended to be larger among women who had not completed four or more years of college, adjusting for race/ethnicity, age at diagnosis, menopausal status, and place of birth (Tables 3 and 5).

With one exception, no racial/ethnic differences were apparent in distribution of the prognostic biomarkers, adjusting for relevant confounders (Tables 2 and 4). Asian women, though, were 3.4 times (95% CI = 1.1, 10.4) more likely than black women and 1.8 times (95% CI = 0.6, 5.2) more likely than white women to be positive for androgen receptor (Table 4). Of the tumors found in all three racial/ethnic groups, approximately 70% were estrogen receptor positive and androgen receptor positive; slightly over half were positive for progesterone receptor, cathepsin D, and Ki67; slightly under 40% were positive for DNA ploidy; about 28% were positive for Her2/neu and for p53; slightly over 20% were positive for ps2; and 13% were positive for epidermal growth factor receptor. No racial/ethnic differences were observed for distributions of tumors that were both estrogen and progesterone receptor negative (age-adjusted odds ratio for black as compared to white women = 1.6 (95% CI = 0.5, 4.6), and for Asian as compared to white women = 0.9 (95% CI = 0.3, 2.9).

No clear patterns of socioeconomic differences were apparent for distribution of breast cancer molecular prognostic biomarkers, adjusted for relevant confounders (Table 5). Estrogen and androgen receptor positive tumors, however, tended to be less common among women with fewer than four years of college education versus women with at least four years of college education, and tumors positive for p53 tended to be more frequent among the less educated women (Table 5).

## Discussion

Our study finds little evidence of racial/ethnic and socioeconomic differences in

TABLE 1.—Selected Sociodemographic, Reproductive, and Anthropometric Variables of 135 Women Diagnosed with Breast Cancer, Overall and by Race/Ethnicity, San Francisco Bay Area, 1966–1990

| Characteristics | | Total (n = 135) | | White (n = 48) | | Black (n = 44) | | Asian (n = 43) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Frequency | (%) | Frequency | (%) | Frequency | (%) | Frequency | (%) |
| Age at diagnosis | <55 years old | 48 | (35.6) | 14 | (29.2) | 14 | (31.8) | 20 | (46.5) |
| | ≥55 years old | 87 | (64.4) | 34 | (70.8) | 30 | (68.2) | 23 | (53.5) |
| Birth place | US-born | 102 | (81.5) | 34 | (73.9) | 36 | (90.0) | 31 | (81.6) |
| | Foreign | 23 | (18.5) | 12 | (26.1) | 4 | (10.0) | 7 | (18.4) |
| Working class (WC) block group | ≥66% WC | 88 | (66.7) | 28 | (60.9) | 34 | (77.3) | 26 | (61.9) |
| | <66% WC | 44 | (33.3) | 18 | (39.1) | 10 | (22.7) | 16 | (38.1) |
| Poverty block group | ≥20% poor | 22 | (16.7) | 2 | (4.3) | 15 | (34.1) | 5 | (11.9) |
| | <20% poor | 110 | (83.3) | 44 | (95.7) | 29 | (65.9) | 37 | (88.1) |
| Level of education | <4 year-college | 106 | (79.1) | 32 | (68.1) | 37 | (84.1) | 37 | (86.0) |
| | ≥4 year-college | 28 | (20.9) | 15 | (31.9) | 7 | (15.9) | 6 | (14.0) |
| Pregnancy history | Ever pregnant | 104 | (77.6) | 38 | (79.2) | 36 | (81.8) | 30 | (71.4) |
| | Never pregnant | 30 | (22.4) | 10 | (20.8) | 8 | (18.2) | 12 | (28.6) |
| Age at menopause | <45 years | 23 | (17.8) | 4 | (8.7) | 17 | (41.5) | 2 | (4.8) |
| | 45–54 years | 66 | (51.2) | 28 | (60.9) | 13 | (31.7) | 25 | (59.5) |
| | ≥55 years | 12 | (9.3) | 5 | (10.9) | 5 | (12.2) | 2 | (4.8) |
| | Premenopausal | 28 | (21.7) | 9 | (19.5) | 6 | (14.6) | 13 | (31.0) |
| Body mass index | <21 | 21 | (16.7) | 3 | (7.0) | 1 | (2.3) | 14 | (36.8) |
| | 21–24 | 51 | (40.5) | 20 | (46.5) | 13 | (31.0) | 18 | (47.4) |
| | ≥25 | 54 | (42.8) | 20 | (46.5) | 28 | (66.7) | 6 | (15.8) |

Note: A small number of women (usually <3%) were missing data for selected characteristics; percentages are based on those with complete data.

TABLE 2.—Selected Tumor Characteristics and Prognostic Biomarkers of 135 Women Diagnosed with Breast Cancer, Overall and by Race/Ethnicity, San Francisco Bay Area, 1966–1990

| Characteristics | | Total (n = 135) | | White (n = 48) | | Black (n = 44) | | Asian (n = 43) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Frequency | (%) | Frequency | (%) | Frequency | (%) | Frequency | (%) |
| Tumor stage | Local | 88 | (65.7) | 29 | (61.7) | 28 | (63.6) | 31 | (72.1) |
| | Regional/distant | 46 | (34.3) | 18 | (38.3) | 16 | (36.4) | 12 | (27.9) |
| Tumor size | <20 mm | 50 | (40.0) | 24 | (58.5) | 14 | (33.3) | 12 | (28.6) |
| | 20–49 mm | 55 | (44.0) | 14 | (34.2) | 18 | (42.9) | 23 | (54.8) |
| | ≥50 mm | 20 | (16.0) | 3 | (7.3) | 10 | (23.8) | 7 | (16.6) |
| Lymph node involvement | Any | 59 | (43.7) | 24 | (50.0) | 19 | (44.2) | 16 | (37.2) |
| | None | 76 | (56.3) | 24 | (50.0) | 24 | (55.8) | 27 | (67.8) |
| Estrogen | ≥10% stained | 94 | (71.8) | 35 | (74.5) | 29 | (69.0) | 30 | (71.4) |
| Progesterone | ≥10% stained | 71 | (54.2) | 27 | (57.4) | 21 | (50.0) | 23 | (54.8) |
| Androgen | ≥10% stained | 90 | (69.2) | 34 | (72.3) | 24 | (58.5) | 32 | (76.2) |
| *EGFR | ≥10% stained | 17 | (13.0) | 5 | (10.6) | 5 | (11.9) | 7 | (16.7) |
| Her2/Neu | ≥10% stained | 37 | (28.5) | 14 | (29.8) | 8 | (19.5) | 15 | (35.7) |
| Cathepsin D | ≥10% stained | 69 | (54.1) | 30 | (63.8) | 18 | (42.9) | 21 | (51.2) |
| P53 | ≥5% stained | 28 | (21.4) | 9 | (19.1) | 7 | (16.7) | 12 | (28.6) |
| Ps2 | ≥10% stained | 35 | (27.6 | 15 | (31.9) | 10 | (25.0) | 10 | (25.0) |
| Ki67 | ≥10% stained | 65 | (50.8) | 22 | (46.8) | 22 | (53.7) | 21 | (52.5) |
| DNA ploidy | ≥8% stained | 45 | (38.5) | 16 | (37.2) | 13 | (34.2) | 16 | (44.4) |

Note: A small number of women (usually <3%) were missing data for selected characteristics; percentages are based on those with complete data.
* EGFR = Epidermal Growth Factor Receptor.

TABLE 3.—Odds Ratios and 95% Confidence Intervals of Tumor Characteristics and Prognostic Biomarkers by Socioeconomic Position, 135 women Diagnosed with Breast Cancer, San Francisco Bay Area, 1966–1990

| Characteristics | | Working Class (WC) Block Group ≥66% WC vs. <66% WC | | Education Level <4 Year-College vs. ≥4 Year-College | |
|---|---|---|---|---|---|
| | | OR | (95% CI) | OR | (95% CI) |
| Tumor size | (≥20 mm vs. <20 mm) | 0.94 | (0.44, 2.00) | 3.33 | (1.40, 7.93) |
| Lymph node involvement | (Any vs. None) | 1.56 | (0.66, 3.68) | 1.21 | (0.45, 3.26) |
| Tumor stage | (Reg./Dist. vs. None) | 1.39 | (0.66, 2.99) | 1.21 | (0.47, 2.75) |
| Estrogen | (+ vs. −) | 1.34 | (0.59, 3.07) | 0.25 | (0.07, 0.90) |
| Progesterone | (+ vs. −) | 2.03 | (0.95, 4.32) | 0.43 | (0.17, 1.07) |
| Androgen | (+ vs. −) | 0.54 | (0.25, 1.19) | 0.34 | (0.11, 1.06) |
| EGFR | (+ vs. −) | 0.85 | (0.28, 2.62) | 0.83 | (0.25, 2.79) |
| Her2/Neu | (+ vs. −) | 1.03 | (0.45, 2.33) | 2.59 | (0.83, 8.13) |
| Cathepsin D | (+ vs. −) | 1.39 | (0.66, 2.92) | 1.31 | (0.56, 3.07) |
| P53 | (+ vs. −) | 0.38 | (0.13, 1.10) | 9.24 | (1.20, 71.40) |
| Ps2 | (+ vs. −) | 1.15 | (0.50, 2.63) | 0.87 | (0.33, 2.34) |
| Ki67 | (+ vs. −) | 0.83 | (0.39, 1.73) | 2.69 | (1.07, 6.80) |
| DNA ploidy | (+ vs. −) | 1.73 | (0.79, 3.77) | 2.72 | (0.93, 7.94) |

distribution of breast cancer molecular prognostic biomarkers among a sample of 135 white, black, and Asian women belonging to a large health maintenance organization in the San Francisco Bay Area. Taking into account potential confounders, however, tumor size varied by race/ethnicity, with size greater among black and Asian as compared to white women. These data suggest that racial/ethnic and socioeconomic disparities in breast cancer survival are unlikely to be explained solely by distributions of breast cancer prognostic biomarkers.

Interpretation of our results is limited by small sample size, thus low power and consequently large confidence intervals for effect estimates. Although confidence intervals for some of the elevated or reduced odds ratios might have excluded 1 were the sample size larger, absence of any clear racial/ethnic or socioeconomic pattern in size and direction of estimates is notable. Moreover, given the many comparisons performed, the observed greater prevalence of androgen receptor positive tumors among Asian as compared to black women might be due to chance.

Other factors affecting interpretation pertain to misclassification and bias concerning race/ethnicity, socioeconomic position, and prognostic biomarkers. Misclassification of race/ethnicity is likely to be small, since data were obtained by self-report. Selection bias related to socioeconomic position may affect the extent to which results can be generalized to other populations, since findings may not be applicable to women without health care coverage. Even so, results should not be biased for women with health-care coverage, since women included in this study were selected randomly from a cohort of women enrolled in a large health maintenance organization. The study population's socioeconomic profile further suggests minimal bias since proportions of women in this study living in predominantly working class and poor block-groups were comparable to those for the general population in the San Francisco Bay Area in the 1980s.[52] Use of census block-group measures of socioeconomic position, however, may have diluted estimates of effects of class position, as compared to measures based on individual-level social class data, and may have resulted in residual con-

TABLE 4.—Odds Ratios and 95% Confidence Intervals of Tumor Characteristics and Prognostic Biomarkers by Racial/Ethnic Group from Logistic Regression, Adjusted for Age at Diagnosis, Menopausal Status, Place of Birth, and Working Class Block-Group Composition, for 135 Women Diagnosed with Breast Cancer, San Francisco Bay Area, 1966–1990

| Characteristics | | Black vs. White | | Asian vs. Black | | Asian vs. White | |
|---|---|---|---|---|---|---|---|
| | | OR | (95% CI) | OR | (95% CI) | OR | (95% CI) |
| Tumor size | (≥20 mm vs. <20 mm) | 3.53 | (1.23, 10.11) | 1.05 | (0.37, 2.98) | 3.72 | (1.31, 10.56) |
| Lymph node involvement | (Any vs. None) | 1.30 | (0.42, 4.07) | 0.62 | (0.20, 1.99) | 0.81 | (0.27, 2.42) |
| Tumor stage | (Reg./Dist. vs. None) | 1.24 | (0.47, 3.31) | 0.47 | (0.17, 1.36) | 0.59 | (0.21, 1.63) |
| Estrogen | (+ vs. −) | 0.82 | (0.28, 2.39) | 1.58 | (0.52, 4.83) | 1.30 | (0.43, 3.89) |
| Progesterone | (+ vs. −) | 0.83 | (0.32, 2.18) | 1.48 | (0.54, 4.03) | 1.23 | (0.47, 3.25) |
| Androgen | (+ vs. −) | 0.52 | (0.19, 1.43) | 3.38 | (1.10, 10.37) | 1.75 | (0.60, 5.15) |
| EGFR | (+ vs. −) | 1.69 | (0.39, 7.27) | 1.12 | (0.28, 4.39) | 1.89 | (0.47, 7.66) |
| Her2/Neu | (+ vs. −) | 0.47 | (0.13, 1.63) | 2.54 | (0.74, 6.77) | 1.19 | (0.41, 3.44) |
| Cathepsin D | (+ vs. −) | 0.48 | (0.18, 1.26) | 1.63 | (0.60, 4.45) | 0.78 | (0.30, 2.06) |
| P53 | (+ vs. −) | 1.83 | (0.49, 6.83) | 1.27 | (0.36, 4.45) | 2.32 | (0.65, 8.35) |
| Ps2 | (+ vs. −) | 0.62 | (0.21, 1.82) | 1.24 | (0.40, 3.83) | 0.76 | (0.26, 2.19) |
| Ki67 | (+ vs. −) | 1.45 | (0.57, 3.74) | 0.84 | (0.31, 2.25) | 1.21 | (0.47, 3.15) |
| DNA ploidy | (+ vs. −) | 1.22 | (0.41, 3.61) | 1.22 | (0.43, 3.51) | 1.00 | (0.33, 3.00) |

founding affecting racial/ethnic comparisons adjusted for socioeconomic position.[52,57] Even so, consistent or strong associations were not observed with available individual-level data on educational level. Lastly, although misclassification of prognostic biomarker status is possible, these data are unlikely to be biased by race/ethnicity or socioeconomic position, since assays were conducted blind to these case characteristics.

Comparison of our results to prior studies of race/ethnicity, socioeconomic position, and breast cancer prognostic biomarkers is complicated by measurement issues involving key study variables. First, epidemiologic analyses of breast cancer prognostic biomarkers employ a variety of assay techniques and also use different cut-points to denote positive results,[7,23–50] rendering comparisons across studies difficult. Nevertheless, biomarker distributions observed in our study are highly consistent with reported positivity in other studies.[7,23–50] Our results provide additional evidence[58,59] that biomarkers from tumors preserved in paraffin blocks for up to 30 years are not compromised by degradation; one implication is that such tumor blocks may be a useful resource for cancer studies requiring data on tumor characteristics and extensive follow-up periods.

A second measurement issue concerns classification of race/ethnicity. Most other studies on race/ethnicity and breast cancer prognostic biomarkers do not state how they measured this key variable.[6,24,43–50] One study, however, reported it classified race/ethnicity based on "appearance, patient questioning, surname, or medical record review."[7] Another stated it obtained data on race/ethnicity from a mixture of personal interviews and hospital records.[25] Our study, by contrast, along with one other,[23] categorized race/ethnicity based on self-identification, as supported by current public health recommendations which recog-

TABLE 5.—Odds Ratios and 95% Confidence Intervals of Tumor Characteristics and Prognostic Biomarkers by Socioeconomic Position from Logistic Regression, Adjusted for Race/Ethnicity, Age at Diagnosis, Menopausal Status, and Place of Birth, for 135 Women Diagnosed with Breast Cancer, San Francisco Bay Area, 1966–1990

| Characteristics | | Working Class (WC) Block Group ≥66% WC vs. <66% WC | | Education Level <4 Year-College vs. ≥4 Year-College | |
|---|---|---|---|---|---|
| | | OR | (95% CI) | OR | (95% CI) |
| Tumor size | (≥20 mm vs. <20 mm) | 1.64 | (0.66, 4.07) | 2.10 | (0.78, 5.62) |
| Lymph node involvement | (Any vs. None) | 2.06 | (0.77, 5.52) | 1.16 | (0.39, 3.41) |
| Tumor stage | (Reg./Dist. vs. None) | 1.82 | (0.77, 4.34) | 1.15 | (0.44, 3.04) |
| Estrogen | (+ vs. −) | 1.40 | (0.53, 3.73) | 0.29 | (0.08, 1.11) |
| Progesterone | (+ vs. −) | 1.65 | (0.70, 3.90) | 0.57 | (0.21, 1.52) |
| Androgen | (+ vs. −) | 0.49 | (0.20, 1.21) | 0.28 | (0.08, 0.94) |
| EGFR | (+ vs. −) | 0.73 | (0.20, 2.62) | 0.62 | (0.17, 2.30) |
| Her2/Neu | (+ vs. −) | 0.68 | (0.25, 1.87) | 1.97 | (0.57, 6.77) |
| Cathepsin D | (+ vs. −) | 1.23 | (0.52, 2.95) | 1.46 | (0.55, 3.86) |
| P53 | (+ vs. −) | 0.39 | (0.11, 1.45) | 7.45 | (0.90, 61.97) |
| Ps2 | (+ vs. −) | 1.17 | (0.46, 2.96) | 1.09 | (0.36, 3.28) |
| Ki67 | (+ vs. −) | 0.90 | (0.39, 2.09) | 2.38 | (0.85, 6.65) |
| DNA ploidy | (+ vs. −) | 2.06 | (0.83, 5.13) | 2.72 | (0.83, 8.90) |

nize that race/ethnicity is a social, not biological, construct.[60–63]

Despite potential differences in racial/ethnic classification, as well as regional differences in composition of racial/ethnic groups, several of our findings are consistent with those reported in prior studies. These include larger tumor size among black as compared to white women,[23] and no black/white differences in distributions of p53,[7,23] DNA ploidy,[7,23] Her2/neu,[7,23] Ki67,[23] epidermal growth factor receptor expression,[23] progesterone receptor status,[23] and estrogen receptor status.[23,50] One investigation also reported no black/white differences for several tumor characteristics not assessed in our study: tumor differentiation, tumor grade, lipid-associated sialic acid, and carcinogenic embryonic antigen level.[23]

In contrast to our results, however, several studies have reported that black women were more likely than white women to have estrogen receptor negative tumors,[7,24,25,44–49] and one found that black women were more likely than white women to have p53 gene alterations associated with poorer prognosis.[6] An additional study also observed black women to be more likely than white women to have a rare allele of the protooncogene h-ras (not examined in our study), which was also associated with younger age at diagnosis, more aggressive tumors, and poorer survival.[64]

Notably, only two of the studies reporting black/white differences in estrogen receptor status included socioeconomic variables in their analyses.[24,25] Whereas one found that controlling for socioeconomic position accounted for black/white differences in estrogen receptor status,[24] the other did not.[25] Differences in results across these two studies and our own may, in part, result from divergent approaches to measuring and analyzing socioeconomic data, as we discuss below, and may also reflect limitations imposed by our small sample size.

First, the study that found socioeconomic position contributed to black/white differences in estrogen receptor status[24] used census tract-based measures, with poverty areas defined as tracts where ≥7% of the population was below the poverty line, less educated areas defined as tracts where ≤67% of the adult population had completed 4

years of high school, and highly educated areas defined as tracts where >11% of the adult population had completed 4 or more years of college. Using these measures, this study found that black and white women residing in census tracts with greater poverty and with less education were more likely to have estrogen receptor negative tumors; adjusting for these socioeconomic measures, in turn, greatly reduced black/white differences in estrogen receptor status.

By contrast, the other investigation obtained data on each woman's educational level, poverty index (ratio of annual family income to poverty level for a family of the same size, multiplied by 100), and occupation.[25] Analyses of socioeconomic differences in estrogen receptor status were first conducted separately among black and white women and were restricted to comparisons of affluent (poverty index >400) to less affluent (poverty index ≤400) women. Notably, whereas 17% of black women and 54% of white women were classified as "affluent" by this measure, 42% of black women and 9% of white women had a poverty index of <126 (meaning they lived below 126% of the poverty line). This study reported that lower socioeconomic position was associated with lower prevalence of estrogen receptors only among breast tumors in white women and, thus, adjusting for this socioeconomic measure did not notably alter the greater likelihood of black women to have estrogen receptor negative tumors. Lack of precision in evaluating socioeconomic position among the black women, along with limited overlap in distributions between the black and white women, may have contributed to these findings. Interestingly, however, a British study examining social class in relation to estrogen receptor status found no difference between poor and affluent white women, using the Carstairs index of deprivation, nor did it detect socioeconomic differences in tumor size, nodal status, or tumor grade.[65]

Taking into account difficulties in measuring both race/ethnicity and socioeconomic position,[60–63] our findings suggest that, despite marked differences in socioeconomic position, white, black, and Asian women have comparable distributions of many breast cancer prognostic biomarkers, other than tumor size. Our study thus lends further support to the hypothesis that experiences associated with race/ethnicity and socioeconomic position contribute to racial/ethnic and socioeconomic disparities in breast cancer survival. Possible factors to consider include co-morbidity and poorer baseline health status, compromised immunologic systems (perhaps reflecting stress-induced changes stemming from racial discrimination and socioeconomic deprivation), and exposure to environmental and occupational agents affecting tumor development.[25,65,66] As a step toward evaluating these hypotheses more definitively, future research should characterize distribution of prognostic biomarkers in larger populations of women diagnosed with breast cancer who are diverse in their racial/ethnic and socioeconomic composition, and should also address their relationship to breast cancer survival, using well-defined and consistent measures of racial/ethnic self-identification, socioeconomic position, and prognostic biomarkers.

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