Patterns of DNA Ploidy and S-Phase Fraction Associated with Breast Cancer Survival in Blacks and Whites


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ABSTRACT

A significant survival difference between black and white breast cancer patients has been observed in the United States. Evaluation of the prognostic value of DNA ploidy and S-phase fraction (SPF) in black and white breast cancer patients may contribute to our understanding of the mechanisms of racial disparity in survival. A sample of 98 patients (50 blacks and 48 whites) who participated in the Black/White Cancer Survival Study was selected for DNA flow cytometry analysis. Patients were followed between 4.5 and 6.5 years. The impacts of DNA ploidy and SPF on breast cancer survival were examined. Kaplan-Meier survival curves, log rank statistics, and Cox proportional hazards regression were used for survival analyses. Black patients were more likely than white patients to have tumors with high SPF (P < 0.05), but there was no difference in DNA ploidy (P = 0.79). Because there were significant interactions of both DNA ploidy and SPF with race, survival was examined separately for blacks and whites. Significantly poorer survival was observed for white patients with class A ploidy (hypodiploid, hypotetraploid, and hypertetraploid; P = 0.001) and with high SPF (P = 0.025). The elevated hazard ratios remained significant after adjusting for age and stage. Further adjustment for adjuvant therapy and histopathological characteristics of tumor reduced the hazard ratios of SPF to a nonsignificant level. No significant associations were found between survival and DNA ploidy or SPF among blacks. DNA ploidy and SPF are prognostic factors for breast cancer survival in white patients but not in blacks. This may have clinical implication in breast cancer management.

INTRODUCTION

A significant survival difference between black and white breast cancer patients has been observed in the United States (1, 2). In addition to a more advanced stage of disease at diagnosis, several hypotheses have been proposed to explain the poor survival of blacks with breast cancer. These include a lower socioeconomic status, fewer cancer-directed treatments, limited access to health care, more prevalent comorbidity, and more aggressive types of tumors among blacks than whites (3–7).

Analysis of tumor ploidy and SPF (3) by DNA flow cytometry has been demonstrated to be a powerful technique in evaluating the DNA content and cell proliferation of breast cancer. Several studies have shown SPF to be associated with breast cancer survival (9, 10). Therefore, evaluation of the prognostic value of DNA ploidy and SPF in black and white breast cancer patients may provide clues to the racial difference in survival. When the DNA ploidy was separated into diploidy and aneuploidy, inconsistent associations had been reported between DNA ploidy and survival (9, 11–14). A revised DNA ploidy classification which better predicts survival has been proposed (11). As a result, a more consistent pattern between DNA ploidy and survival was observed when DNA ploidy was classified by the DI (10–12, 15, 16). Diploidy, near-hyperdiploidy, and tetraploidy have been associated with a better survival (10, 12, 15), whereas a significantly poorer survival has been observed in breast cancer patients with hypodiploidy, hypotetraploidy, and hypertetraploid tumors (11, 15, 16). Hypodiploidy and hypotetraploidy have been associated with large tumor size, high histological grade, and low expression of the ER and PR (15, 16). Hypertetraploid tumors tend to have large tumor size and advanced tumor stage (11). A prognostic value has not been established yet for multiploid tumors (13). In contrast to DNA ploidy, high SPF has been widely accepted to be a significant indicator for breast cancer survival (13, 17, 18) and has been reported to be associated with nuclear grade, tumor size, ER, PR, lymph node metastasis, and age (12, 15, 17).

In this study, we examined the associations of DNA ploidy and SPF with known prognostic factors. We further investigated their impact on breast cancer survival and contribution to black/white survival disparity.

The abbreviations used are: SPF, S-phase fraction; BAD, background-aggregate-debris; DI, DNA index; ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor.
**MATERIALS AND METHODS**

**Study Subjects.** Study subjects were selected from 209 cases of stage I and II breast adenocarcinomas from the metropolitan New Orleans area, accrued as part of the National Cancer Institute Collaborative Black/White Cancer Survival Study (19). Eligible subjects were women, ages 20–79, diagnosed with breast cancer between January 1, 1985 and December 31, 1986. Data available for analysis (Table 1) include ER and PR, first course of treatment, a central histopathological evaluation of tumor, and a summary stage assigned by a working group, as described previously (20).

Survival information was obtained by record linkage with the state’s mortality files; by review of data from hospital tumor registries and hospital admissions subsequent to the initial diagnosis; and by contacting patients, their relatives, or physicians. All patients were followed through June 30, 1991, providing a follow-up of 4.5–6.5 years for each patient. Breast cancer-specific mortality was the outcome of primary interest, and death from other causes was censored in the survival analysis.

Five major hospitals in the study area were selected to participate in this DNA ploidy and SPF study because of ongoing collaboration and availability of specimens. One hundred one cases of formalin-fixed, paraffin-embedded tissue blocks were obtained for flow cytometry analysis. Three cases with more than 20% BAD% in flow cytometry analysis were excluded, resulting in 98 cases in the final analysis: 50 blacks and 48 whites. Potential bias due to this selection process was evaluated by comparing the relationship between race and selected prognostic factors from the study sample with results from all eligible subjects (Table 1). The racial (black/white) distributions of prognostic factors were very similar in the two populations.

**Table 1** Black/white distributions of selected prognostic factors among all eligible subjects and study sample

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>All eligible subjects (%)</th>
<th></th>
<th>Study sample (%)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Blacks (n = 91)</td>
<td>Whites (n = 118)</td>
<td>P</td>
<td>Blacks (n = 50)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
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<tr>
<td>I</td>
<td>19.8</td>
<td>35.6</td>
<td>0.017</td>
<td>14.0</td>
</tr>
<tr>
<td>II (N0)</td>
<td>37.3</td>
<td>22.9</td>
<td>0.017</td>
<td>34.0</td>
</tr>
<tr>
<td>II (N1)</td>
<td>42.9</td>
<td>41.5</td>
<td>0.017</td>
<td>52.0</td>
</tr>
<tr>
<td>Age (yr)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;50</td>
<td>39.6</td>
<td>43.2</td>
<td>0.017</td>
<td>28.0</td>
</tr>
<tr>
<td>≥50</td>
<td>60.4</td>
<td>56.8</td>
<td>0.017</td>
<td>72.0</td>
</tr>
<tr>
<td>Nuclear atypia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>35.8</td>
<td>44.6</td>
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<td>40.9</td>
</tr>
<tr>
<td>Moderate and high</td>
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<td>55.4</td>
<td>0.017</td>
<td>59.1</td>
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<td>(11.0)%</td>
<td>(5.1)%</td>
<td></td>
<td>(11.8)%</td>
</tr>
<tr>
<td>Mitotic activity</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>55.7</td>
<td>54.1</td>
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<td>58.1</td>
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<td>Unknown</td>
<td>(13.2)%</td>
<td>(7.6)%</td>
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<td>(13.7)%</td>
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<tr>
<td>Tubule formation</td>
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<tr>
<td>Few</td>
<td>81.3</td>
<td>67.9</td>
<td>0.017</td>
<td>75.0</td>
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<td>32.1</td>
<td>0.017</td>
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<td>Unknown</td>
<td>(12.1)%</td>
<td>(5.1)%</td>
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<td>(11.8)%</td>
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<tr>
<td>Histological grade</td>
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<td>Well</td>
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<td>(5.1)%</td>
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<td>38.5</td>
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<td>61.5</td>
<td>0.017</td>
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<td>(22.9)%</td>
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<td>(17.6)%</td>
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<td>Chemotherapy</td>
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<td>76.3</td>
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<td>18.7</td>
<td>23.7</td>
<td>0.017</td>
<td>12.0</td>
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<td>Radiation therapy</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>No/unknown</td>
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<td>68.6</td>
<td>0.017</td>
<td>78.0</td>
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<td>Yes</td>
<td>27.5</td>
<td>31.4</td>
<td>0.017</td>
<td>22.0</td>
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<td>Hormone therapy</td>
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<td></td>
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<tr>
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<td>83.5</td>
<td>81.4</td>
<td>0.017</td>
<td>70.0</td>
</tr>
<tr>
<td>Yes</td>
<td>16.5</td>
<td>18.6</td>
<td>0.017</td>
<td>30.0</td>
</tr>
</tbody>
</table>

*P values are χ² test for frequency distributions between blacks and whites.

*N*₀, without lymph node involved; *N*₁, with lymph node involved.

Numbers in parentheses, percentage of total.
groups. The only exceptions were that in the study sample, blacks tended to be older while whites were more likely to have chemotherapy and radiation therapy than all eligible subjects.

**Tissue Preparation.** Tissue blocks containing >20% of tumor and normal cells were selected for flow cytometry. A serial 50-μm section was dewaxed in three changes of xylene (10 min each) and rehydrated sequentially through gradient ethanol (two changes of 100%, two changes of 95%, one bath of 75%, and one bath of 50%) with 10 min in each step. The section was then soaked in two changes of 100% ethanol for 20 min. Rehydrated tissues were digested with 1 ml of Subtilisin Carlsberg XX IV (P8038; Sigma, St. Louis, MO) enzyme solution (0.1% enzyme, 0.1 M Tris base, 0.07 M NaCl, pH 7.2) at 37°C for 2 h (21). After digestion, tubes were vortexed vigorously for 2 min at room temperature to dissociate the nuclei. Nuclei solution was then filtered through a 37-μm nylon mesh. A drop of 2 μl of nuclei solution was dried on a glass slide by heating and counterstained with hematoxylin for the evaluation of nuclei representativeness and aggregation. Nuclei solution (5 × 10^5 nuclei/ml) was then incubated with RNase (0.1 mg/ml, R5000; Sigma) and propidium iodide (50 μg/ml, Calbiochem 537059; Calbiochem-Novabiochem Co., La Jolla, CA) at 4°C overnight. Samples were gently shaken at room temperature for at least 30 min prior to flow cytometric analysis.

**Flow Cytometry.** Propidium iodide-stained samples were measured at 488 nm on an EPICS Profile (Coulter, Hialeah, FL) flow cytometer equipped with an air-cooled 20-mW argon laser. A total of 20,000 nuclei were collected for each DNA analysis. The nuclei were selected by pulse-height (doublet elimination) analysis and only the integrated signals were collected to reject doublets. All histograms were analyzed by Multicycle software (version 2.53; Phoenix Flow Systems, San Diego, CA; Ref. 22). The G0−G1 and G2−M peaks were determined using Gaussian curves. χ² statistics were used to evaluate goodness-of-fit between the computer-generated curve and raw data. Diploid G0−G1 peak was identified as a single G0−G1 peak or the taller peak if two close G0−G1 peaks were encountered. Tumors were considered as nondiploid if two or more distinct G0−G1 peaks with corresponding G2−M peaks were detected. DI was obtained from the ratio of the mean channel number of diploid G0−G1 peaks and that of nondiploid G0−G1 peaks.

Tumor ploidy was categorized into two groups according to DI as recommended by other investigators (11, 13, 16): class A ploidy, including hypodiploidy, hypotetraploidy, and hypertetraploidy, and class B ploidy, consisting of diploidy, near-hypotetraploidy, and tetraploidy. Multiploid tumors, which have more than one nondiploid peak, were categorized as class A ploidy if at least one cell population is hypodiploid, hypotetraploid, or hypertetraploid; otherwise, they were considered as class B ploidy. The lymphocytes or normal epithelial cells coexisting with tumor cells in the same section provide a natural internal ploidy control.

The SPF was calculated by the area under the zero-order polynomial curve between the mean channel number of G0−G1 peak and that of the G2−M peak. An average SPF value was determined according to the proportion (weight) of nuclei in the diploid and aneuploid populations. For tumors with percentage of BAD% over 20%, the analysis for SPF was rejected (23). Using the median SPF, cases were dichotomized into high and low SPF.

**Statistical Analysis.** The distributions of prognostic factors in blacks and whites were compared using frequency tables and evaluated using χ² tests of independence. The associations of DNA ploidy and SPF with age, stage, and tumor characteristics (nuclear atypia, mitotic activity, tubule formation, histological grade, ER, and PR) were evaluated by χ² statistics. Kaplan-Meier product limit estimates of survival probabilities from breast cancer were calculated for black and white patients by DNA ploidy and SPF (24). Log rank statistics were used to test for the significance of survival differences (25). In addition, multivariate modeling using Cox proportional hazards regression (26) was used to determine the significance of DNA ploidy and SPF on survival after adjusting for other prognostic factors, including stage and treatment.

**RESULTS**

**DNA Ploidy in Whites and in Blacks, and Their Associations with Prognostic Factors.** The distribution of cases by class of DNA ploidy is shown in Table 2. About 37% (36/98) of the study subjects had class A ploidy tumors which are associated with a less favorable survival. The proportions of class A ploidy did not vary significantly by race, 35.4% in whites versus 38.0% in blacks. Seven cases of multiploidy were considered as class A ploidy because at least one cell population

<table>
<thead>
<tr>
<th>Class of ploidy</th>
<th>Blacks (n = 50)</th>
<th>Whites (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypodiploidy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DI &lt; 1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>1.4 ≤ DI &lt; 1.9</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Hypotetraploidy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DI &gt; 2.1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Multiploidy†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>more than two populations</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Class B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diploidy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>single population</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Near-hypotetraploidy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 &lt; DI &lt; 1.4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Tetraploidy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.9 ≤ DI ≤ 2.1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

† At least one population was detected as hypodiploidy, hypotetraploidy, or hypertetraploidy.
was detected having hypodiploidy, hypotetraploidy, or hyper-
tetraploidy.

When examining the relationship between class of ploidy
and known prognostic factors, we did not find a significant
association of class A ploidy with prognostic factors among
white patients. However, class A ploidy was more frequently
detected in black patients with tumors of higher nuclear atypia
\( (P < 0.05) \) and mitotic activity \( (P < 0.05) \).

**SPF in Whites and in Blacks, and Their Associations
with Prognostic Factors.** The SPF of the 98 cases ranged
from 0.3 to 18.0%, with a median of 3.6%. When cases were
separated into high SPF (greater than the median) and low SPF
(equal to or less than the median), 39.6% (19/48) white patients
had breast tumors with high proliferation, whereas 60% (30/50)
black patients did. This excess of high SPF tumors among
blacks is statistically significant \( (P < 0.05) \). In addition, high
SPF was significantly \( (P < 0.05) \) associated with higher mitotic
activity, higher histological grade, and class A DNA ploidy in
both races; with higher nuclear atypia and ER in whites only;
and with PR in blacks only.

**Associations of DNA Ploidy and SPF with Survival.**
All 98 patients were traced through June 30, 1991 with no loss
to follow-up. A total of 17 breast cancer deaths (8 whites and 9
blacks) occurred during the follow-up period. Additionally, 12
patients (3 whites and 9 blacks) died from other causes, includ-
ing one whose cause of death was unknown, and were censored
in the survival analysis.

No significant difference in breast cancer survival was
observed between black and white patients at the current stage
of follow-up. The HR for blacks compared with whites was 0.90
\( (95\% \text{ CI}, 0.33-2.42) \). Adjustment for age and stage had little
impact on the ratio, HR = 0.89. When DNA ploidy and SPF
were added independently to the Cox model, the HRs were
reduced to 0.79 and 0.59, respectively, but remained statistically
nonsignificant. Further inclusion of the interaction terms with
race (DNA ploidy * race and SPF * race) in the models showed
either a significant interaction or a sizable change in the HR.
This suggests that the associations of DNA ploidy and SPF with
survival were differential by race and were, therefore, evaluated
separately for whites and blacks.

Distinct survival patterns by class of ploidy were observed
for white and black patients. Among whites, 41.2% (7/17) of the
patients with class A ploidy died from breast cancer whereas
only 3.2% (1/31) of the patients with class B ploidy did. Log
rank statistics showed a significant association between class A
ploidy and survival \( (P = 0.001) \). Kaplan-Meier survival curves
illustrate that the deficit in survival probability among white
patients with class A DNA ploidy began less than 2 years after
diagnosis (Fig. 1A). In contrast, no significant association be-
 tween DNA ploidy and survival was observed for black patients
(Fig. 1B), with 15.8% (3/19) of class A ploidy patients and
19.4% (6/31) of class B ploidy patients dying from breast
cancer, respectively.

Results of proportional hazard models show that white
women with class A ploidy breast cancer had about 15-fold
excess risk of dying from breast cancer \( (HR = 14.8, 95\% \text{ CI},
1.8-120.9) \) compared with white women with class B ploidy
tumors. The HR was increased to 18.1 (95% CI, 2.14–152.57)
after controlling for age and stage. The excess risk remained
when chemotherapy, radiation therapy, and histopathological
characteristics of tumor were added to the model. Due to limited
number of breast cancer deaths, further adjustment for ER and
PR was not performed. Analysis for blacks did not reveal the
same risk as that observed in whites. The HR associated with
DNA ploidy was 0.75 (95% CI, 0.18–3.02) and controlling for
age, stage, adjuvant therapy, and other prognostic factors did not
change the nonsignificant association between DNA ploidy and
survival in blacks.

A similar, but less pronounced, pattern was observed for
survival and SPF. Among whites, 31.6% (6/19) of the patients
with high SPF died from breast cancer compared with only 6.9%
(2/29) of the patients with low SPF, and the difference in
survival experience was significant \( (P = 0.025, \text{ Fig. 2A}) \).
Although a poorer survival was also observed for blacks with high
SPF tumors, the association did not reach a significant level
(Fig. 2B). About 23% (7/30) of the black patients with high SPF
tumors died from breast cancer whereas only 10% of the black
patients with low SPF tumors died during the same period.

Results from multivariate modeling showed that white
patients diagnosed with breast cancer of high SPF had a 5-fold

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**Figure 1** Survival experience (breast cancer-specific mortality) by class
of DNA ploidy, stratified by race.
DISCUSSION

Although hypodiploid, hypotetraploid, and hypertetraploid (class A ploidy) tumors and tumors with high SPF have been associated with a poorer survival for breast cancer (11, 15, 16), the prognostic values of DNA ploidy and SPF by race have not been investigated. This study is the first to observe distinct racial differential patterns in the associations of breast cancer survival with class A ploidy and SPF.

The significant association of breast cancer survival with class A ploidy tumors in whites which persists even after adjusting for stage, treatments, and other prognostic factors suggests that class A ploidy can be an independent predictor for breast cancer survival in whites. The strong tendency of class A ploidy to coexist with higher nuclear atypia and mitotic activity, observed only in blacks, suggests that breast cancers may follow a different tumorigenic pathway by race. Similarly, high SPF predicts survival for whites but not for blacks, although an excess of high SPF tumors among blacks has been observed in this and other (27) studies. These findings are concordant with our previous report that there is a racial disparity in the association of p53 alterations with breast cancer survival (20). To our knowledge, no studies have reported different prognostic values for the same tumor characteristics among races. The reason could be that the frequencies of prognostic factors were usually compared to evaluate the racial difference in survival. Here, we demonstrate the importance of stratified analysis by race in the study of breast cancer survival.

Although we have detected a racial difference in the associations of DNA ploidy and SPF with breast cancer survival, limitations of the study should be noted. The study is based on a small sample size (98 patients) with few events (17 breast cancer deaths) and some fairly large effects cannot be confidently ruled out. An additional limitation is the lack of data on other confounders which may be associated with DNA ploidy, SPF, and/or survival, such as family history of breast cancer, use of exogenous estrogen, and comorbidity of patients. In spite of these limitations, the present study has numerous strengths. Guidelines (13, 23) from a consensus conference for DNA flow cytometry were followed throughout the whole study to control analytical variations. Samples having BAD% over 20% (three cases) were excluded for SPF analysis. The median of the entire study sample was selected to be the cutoff point for SPF. The choice of the median (3.6%) in this series appears to be appropriate because it separated the study subjects into groups with distinct prognosis, as defined by the established prognostic factors.

The findings of this study, if confirmed by others, could have clinical implications. It has been reported that tumors displaying aneuploidy and a high proliferation index respond well to chemotherapy (28–30). If the impact of DNA ploidy and SPF on survival is truly differential by race, decisions on treatment protocol and patient management may vary depending on the race of the patient and tumor biology such as DNA ploidy, SPF, and p53 alterations. The postulate of a racial difference in treatment response is supported by a previous report that breast cancer survival is different between black and white patients, although they are followed up with the same treatment protocol (31).

Significant associations of DNA ploidy and SPF with breast cancer survival in whites, but not in blacks, were detected in a pilot study of a relatively small sample size. The nature and the mechanism of the difference are unknown, but it may have a practical consequence in terms of treatment selection. Future studies with a larger sample size in this research area are needed.
ACKNOWLEDGMENTS

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Patterns of DNA ploidy and S-phase fraction associated with breast cancer survival in blacks and whites.


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