Background: The lower breast cancer incidence in minority women and the higher breast cancer mortality in African American women than in white women are largely unexplained. The influence of breast cancer risk factors on these differences has received little attention. Methods: Racial/ethnic differences in breast cancer incidence and outcome were examined in 156,570 postmenopausal women participating in the Women’s Health Initiative. Detailed information on breast cancer risk factors including mammography was collected, and participants were followed prospectively for breast cancer incidence, pathological breast cancer characteristics, and breast cancer mortality. Comparisons of breast cancer incidence and mortality across racial/ethnic groups were estimated as hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox proportional hazard models. Tumor characteristics were compared as odds ratios (ORs) and 95% confidence intervals in logistic regression models. Results: After median follow-up of 6.3 years, 3938 breast cancers were diagnosed. Age-adjusted incidences for all minority groups (i.e., African American, Hispanic, American Indian/Alaskan Native, and Asian/Pacific Islander) were lower than for white women, but adjustment for breast cancer risk factors accounted for the differences for all but African Americans (HR = 0.75, 95% CI = 0.61 to 0.92) corresponding to 29 cases and 44 cases per 10,000 person years for African American and white women, respectively. Breast cancers in African American women had unfavorable characteristics; 32% of those in African Americans but only 10% in whites were both high grade and estrogen receptor negative (adjusted OR = 4.70, 95% CI = 3.12 to 7.09). Moreover, after adjustment for prognostic factors, African American women had higher mortality after breast cancer than white women (HR = 1.79, 95% CI = 1.05 to 3.05) corresponding to nine and six deaths per 10,000 person-years from diagnosis in African American and white women, respectively. Conclusion: Differences in breast cancer incidence rates between most racial/ethnic groups were largely explained by risk factor distribution except in African Americans. However, breast cancers in African American women more commonly had characteristics of poor prognosis, which may contribute to their increased mortality after diagnosis. [J Natl Cancer Inst 2005;97:439–48]

Recent data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program indicate that the age-adjusted breast cancer incidence rates for women of racial/ethnic minority groups are substantially lower than those for white women, with 141 cases per 100,000 in white women, 122 in African Americans, 97 in Asian/Pacific Islanders, 90 in Hispanics, and 58 in American Indians/Alaskan Natives (1,2).

In addition, African American women are likelier to be diagnosed at a more advanced stage (2) and to have larger tumors that are more commonly estrogen receptor negative (3,4) and high grade (3–6) than those in white women. African American women also have higher breast cancer mortality than white women (7). All these differences remain largely unexplained (8).

The influence of breast cancer risk factor distribution on differences in incidence and clinical characteristics associated with ethnicity/race has received limited attention (9). Consequently, we explored these relationships in a cohort from the ethnically diverse Women’s Health Initiative (WHI) study (10). Our primary aim was to examine whether known and/or presumptive breast cancer risk factors would explain the difference in breast cancer incidence between white women and women of minority groups. Our secondary aims were to describe the pathologic features of cancers diagnosed in the various racial/ethnic groups and to compare breast cancer mortality in African American and white women.

**METHODS**

**Study Population**

The WHI is a large longitudinal study of postmenopausal women’s health. It includes an observational study and randomized clinical trials that are evaluating effects on clinical outcomes of estrogen plus progestin, estrogen alone, dietary modification, and calcium and vitamin D supplementation (10,11). Women were recruited at 40 clinical centers across the United States, largely through direct mailings (12). Women were eligible to participate if they were postmenopausal, aged 50 to 79 years, unlikely to move or to die within 3 years, and provided written informed consent. The clinical trials had additional eligibility requirements related to safety, competing risks, and potential adherence. In addition, all clinical trials excluded women with a breast cancer history and required that the baseline mammogram
and clinical breast exam not be suspicious for breast cancer. Neither baseline mammogram nor clinical breast exam was required for participation in the observational study.

In general, potential WHI participants were recruited into the clinical trial component. Women who were not interested in being randomly assigned to an intervention or who were ineligible for the clinical trial component were offered enrollment in the observational study. Although women were not excluded from clinical trials based on breast cancer risk factors, the opportunity to self-select the type of participation resulted in some variation in risk factor distributions between study components, with women participating in the hormone clinical trials having fewer breast cancer risk factors than participants in the other trials (data not shown).

A total of 161,809 participants enrolled in either the observational study (N = 93,676) or clinical trial (N = 68,133) components of the WHI between October 1, 1993, and December 31, 1998 (13). Of these, 5,238 women reported a history of breast cancer or mastectomy at baseline. Although these women were eligible for participation in the observational study, they were excluded from this analysis, leaving 156,570 women.

Human Subjects Review Committees at each participating institution approved the WHI study protocol.

**Baseline Data Collection**

Baseline self-administered questionnaires were used to collect information on demographics; medical, reproductive, and family history; personal habits such as smoking and alcohol use; and physical activity as metabolic equivalents. Food intakes were assessed using a semiquantitative food frequency questionnaire (14). Body mass index (BMI) was calculated as weight (kg)/height (m)².

Information about use of postmenopausal hormone therapy, oral contraceptives, medications, and dietary supplements was collected during in-person interviews. Hormone therapy users (past and current) were defined as those who used estrogen-containing pills or patches after menopause for at least 3 months. Current users were using hormone therapy at baseline and/or were randomly assigned to the hormone arms of the two WHI menopausal hormone therapy trials (15). Hormone use was further classified as use of estrogen alone or of combined estrogen plus progesterin.

By self-report, women identified their ethnicity/race selecting from six offered categories: American Indian/Alaskan Native; Asian/Pacific Islander; Black/African American; Hispanic; white; and Unknown.

**Follow-Up and Breast Cancer Ascertainment**

Medical history was updated annually (for women in the observational study) or semiannually (for women in the clinical trials) by mail and/or telephone questionnaires. For women in the clinical trial component of the WHI, the frequency of clinical breast exam and mammography was protocol defined as occurring annually for women in hormone trials and biennially for women in the dietary trial. For women in the observational study, clinical breast exam and mammography were not protocol defined. Information regarding frequency of clinical breast exam and mammography was collected annually from all participants.

Breast cancers were verified by medical record and pathology report review by centrally trained WHI physician adjudicators (16,17). Central adjudication and coding of histology, extent of disease, and estrogen receptor (ER) and progesterone receptor (PR) status (positive or negative per pathology report) were performed at the Clinical Coordinating Center using the SEER coding system (18). Only invasive breast cancer cases confirmed by central review were included.

**Statistical Analyses**

Descriptive analyses were conducted for breast cancer risk factors and other covariates by racial/ethnic groups and by breast cancer status in each group. Model development focused on determining the extent to which breast cancer risk factors and other covariates accounted for differences in breast cancer incidence rates among racial/ethnic groups. To this end, we fit a series of nested proportional-hazard models to assess the association between ethnicity and risk of breast cancer after accounting for established and putative risk factors. The initial set of models provided age-adjusted comparisons of breast cancer incidence among racial/ethnic groups. The second set of models incorporated established risk factors used in the Gail model (19) (age; number of first-degree relatives with breast cancer; ages at menarche, first birth, and menopause; and prior breast biopsy for benign breast disease). The final set of models incorporated other breast cancer risk factors and covariates, including educational level; income level; health insurance status; number of second-degree relatives with breast cancer; BMI; physical activity at baseline and at 18 years of age; alcohol intake; smoking status; parity; total months of breast feeding; prior or current use of oral contraceptives, of non-steroidal anti-inflammatory drugs, and of hormone therapy (HT); dietary intakes, including energy intake from fat; folic acid intake; bilateral oophorectomy and or hysterectomy status; hormone therapy × BMI interaction; history of mammography; and mammography during follow-up (as a time-dependent covariate). Wald chi-square tests were used to test whether individual hazard ratios comparing minority groups to whites (referent category) were different from unity and for a global test to determine if any of these hazard ratios were different from unity.

To adjust for potential effects of age and study design, the proportional-hazards models were stratified by 5-year age groups, hormone therapy use, and clinical trial versus observational study participation. Further adjustments included fitting both categorical and linear terms for BMI and a linear term for age, in addition to the age stratification. Potential effect modification between race/ethnicity and risk factors was examined using tests for each interaction calculated from the final model. The power to detect such interactions was low, given the small number of breast cancers occurring among some groups of minority women.

Because inferences from this model rely on the use of the multivariable Cox regression models, the assumption of proportionality was examined using a two-step procedure. The initial step involved fitting a flexible Cox regression model that allowed both baseline incidence rates and effects of known risk factors to differ among ethnic groups, \( r_i(z) = r_0(t)\exp(zB_0) \), where \( y \) represents ethnicity, \( z \) represents a vector of known risk factors, and \( B_0 \) represents an ethnicity-specific regression coefficient. A score test was then used to determine whether the effects of established risk factors differed for African Americans, Hispanics, or Asian/Pacific Islanders compared with whites. (Insufficient sample size precluded comparative testing of American Indians/Alaskan Natives.) In a second step, we verified the proportional hazards assumption by visually
comparing cumulative baseline incidence rates, \( \int_0^t r_0(u) \, du \), and testing whether there was a statistically significant interaction between time and ethnicity under the assumption of a common baseline incidence function. Because there was no evidence that \( r_0(u) \) differed among ethnic groups, a common baseline incidence function was subsequently used.

Missing data were handled via a procedure known as complete case analysis. To examine the possible impact of missing data, we compared rates of missing data by race/ethnicity. Differences among racial/ethnic groups in rates of missing data were detected for several variables, including age at menopause, family history of breast cancer, prior benign breast disease, and income level. With the exception of income, the missing data were considered to be missing at random (MAR), after taking race/ethnicity into account. Under the MAR assumption, a sensitivity analysis was performed using multiple imputation. Covariate data were imputed five times, regression models were fit, and the resulting parameter estimates were combined [via SAS PROC MI and PROC MIANALYZE, as described by Rubin (20)]. The combined imputation results (not presented) agreed with our main complete case analysis; the breast cancer hazard ratios for each racial/ethnic group compared with white women were all less than 1 but were statistically significant only for African Americans.

For analysis of women diagnosed with invasive breast cancer, logistic regression models were used to explore associations between race/ethnicity and tumor characteristics, after adjustment for age, BMI, hormone therapy use, health insurance status, income level, and educational level. When evidence of racial differences in tumor characteristics was found, multivariable Cox regression models were fit to compare incidence rates of disease subtypes. Comparisons of survival after breast cancer diagnosis between racial/ethnic subgroups were based on a proportional hazards model that was stratified by age, enrollment in the observational study versus clinical trial component, and cancer stage at diagnosis, with age (linear) and BMI (categorical and linear) as covariates. All analyses were conducted using SAS version 9.00. All statistical tests were two-sided.

**RESULTS**

Baseline characteristics for this cohort of 156,570 postmenopausal women by ethnicity are presented in Table 1. African American, Hispanic, and American Indian/Alaskan Native women among the women with breast cancer within each ethnic group are compared to white women. Women with a family history of breast cancer, current or past hormone therapy use, and differences in socioeconomic status (including income) are summarized in Table 1.

**Table 1.** Baseline characteristics and breast cancer risk factors by race/ethnicity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>White</th>
<th>African American</th>
<th>Hispanic</th>
<th>American Indian/Alaskan Native</th>
<th>Asian/Pacific Islander</th>
<th>Unknown</th>
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<tbody>
<tr>
<td></td>
<td>(N = 129,037)</td>
<td>(N = 14,170)</td>
<td>(N = 6,388)</td>
<td>(N = 696)</td>
<td>(N = 4,114)</td>
<td>(N = 2,165)</td>
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<tr>
<td>Age at menarche, y</td>
<td>117,134</td>
<td>27,732</td>
<td>22,887</td>
<td>28,506</td>
<td>11,134</td>
<td>4,600</td>
</tr>
<tr>
<td>&lt;12</td>
<td>27,732</td>
<td>22,887</td>
<td>28,506</td>
<td>11,134</td>
<td>4,600</td>
<td></td>
</tr>
<tr>
<td>≥12</td>
<td>89,081</td>
<td>74,649</td>
<td>23,621</td>
<td>18,652</td>
<td>6,438</td>
<td>1,580</td>
</tr>
<tr>
<td>Age at first birth, y</td>
<td>14,868</td>
<td>14,589</td>
<td>15,070</td>
<td>16,891</td>
<td>13,128</td>
<td>10,460</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>14,868</td>
<td>14,589</td>
<td>15,070</td>
<td>16,891</td>
<td>13,128</td>
<td>10,460</td>
</tr>
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<td>15,070</td>
<td>16,891</td>
<td>13,128</td>
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<tr>
<td>≥20</td>
<td>28,867</td>
<td>46,792</td>
<td>28,968</td>
<td>26,909</td>
<td>15,678</td>
<td>10,768</td>
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<td>Age at screening, mean (SD)</td>
<td>63.5 (7.2)</td>
<td>61.5 (7.1)</td>
<td>60.2 (6.8)</td>
<td>61.5 (7.5)</td>
<td>63.0 (7.5)</td>
<td>63.6 (7.4)</td>
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<tr>
<td>BMI, kg/m²</td>
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<td>60.2 (6.8)</td>
<td>61.5 (7.5)</td>
<td>63.0 (7.5)</td>
<td>63.6 (7.4)</td>
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<td>No. of 1st-degree relatives with breast cancer before age 45</td>
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<td>10,245</td>
<td>16,479</td>
<td>1,697</td>
<td>37,454</td>
<td>102,344</td>
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<td>0</td>
<td>0</td>
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<td>16,479</td>
<td>1,697</td>
<td>37,454</td>
<td>102,344</td>
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<td>≥2</td>
<td>28,767</td>
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<td>28,506</td>
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<td>23,621</td>
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<td>1,580</td>
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(Table continues)
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<tr>
<th>Characteristic</th>
<th>White (N = 129037)</th>
<th>White (N = 14170)</th>
<th>Hispanic (N = 6388)</th>
<th>Hispanic (N = 696)</th>
<th>American/Alaskan Native (N = 4114)</th>
<th>American/Alaskan Native (N = 4114)</th>
<th>Unknown (N = 2165)</th>
<th>Unknown (N = 2165)</th>
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<tr>
<td>0–8 years</td>
<td>844 0.7</td>
<td>435 3.1</td>
<td>1159 18.1</td>
<td>51 7.3</td>
<td>76 1.9</td>
<td>47 2.2</td>
<td></td>
<td></td>
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<tr>
<td>Some high school</td>
<td>3642 2.8</td>
<td>1260 8.9</td>
<td>595 9.3</td>
<td>62 8.9</td>
<td>134 3.3</td>
<td>117 5.4</td>
<td></td>
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<tr>
<td>High school diploma/GED School after</td>
<td>22656 17.6</td>
<td>1950 13.8</td>
<td>1015 15.9</td>
<td>113 16.2</td>
<td>651 15.8</td>
<td>406 18.8</td>
<td></td>
<td></td>
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<tr>
<td>College degree or higher</td>
<td>48787 37.8</td>
<td>5454 38.5</td>
<td>2193 34.3</td>
<td>311 44.7</td>
<td>1427 34.7</td>
<td>865 40.0</td>
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<td></td>
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<tr>
<td>Mammmogram in last 2 years?</td>
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<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>105894 82.1</td>
<td>10727 75.7</td>
<td>4313 67.5</td>
<td>498 71.6</td>
<td>3323 80.8</td>
<td>1700 78.5</td>
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<td>&lt;.001</td>
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<tr>
<td>Mammmogram ever?</td>
<td>124399 96.4</td>
<td>13341 94.2</td>
<td>5703 89.3</td>
<td>640 92.0</td>
<td>3930 95.5</td>
<td>2065 95.4</td>
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<tr>
<td>No. of full-term pregnancies</td>
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<tr>
<td>Nulliparous</td>
<td>14838 11.5</td>
<td>1887 13.3</td>
<td>678 10.6</td>
<td>50 7.2</td>
<td>607 14.8</td>
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<tr>
<td>1</td>
<td>10368 8.0</td>
<td>2107 14.9</td>
<td>537 8.4</td>
<td>81 11.6</td>
<td>375 9.1</td>
<td>218 10.1</td>
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<td>2</td>
<td>32649 25.3</td>
<td>3196 22.6</td>
<td>1261 19.7</td>
<td>131 18.8</td>
<td>1179 28.7</td>
<td>494 22.8</td>
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<td>3</td>
<td>32096 24.9</td>
<td>2539 17.9</td>
<td>1302 20.4</td>
<td>164 23.6</td>
<td>990 24.1</td>
<td>489 22.6</td>
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<td>4</td>
<td>20121 15.6</td>
<td>1715 12.1</td>
<td>1012 15.8</td>
<td>104 14.9</td>
<td>527 12.8</td>
<td>347 16.0</td>
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<tr>
<td>≥5</td>
<td>18254 14.2</td>
<td>2582 18.2</td>
<td>1492 23.4</td>
<td>160 23.0</td>
<td>416 10.1</td>
<td>334 15.4</td>
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<tr>
<td>Alcoholic drinks per day</td>
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<tr>
<td>Nondrinker</td>
<td>49145 38.1</td>
<td>9083 64.1</td>
<td>3646 57.1</td>
<td>382 54.9</td>
<td>2977 72.4</td>
<td>1086 50.2</td>
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<tr>
<td>≤1</td>
<td>62783 48.7</td>
<td>4457 31.5</td>
<td>2422 37.9</td>
<td>261 37.5</td>
<td>1010 24.6</td>
<td>894 41.3</td>
<td></td>
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<tr>
<td>&gt;1 to ≤2</td>
<td>11302 8.8</td>
<td>363 2.6</td>
<td>190 3.0</td>
<td>34 4.9</td>
<td>88 2.1</td>
<td>111 5.1</td>
<td></td>
<td></td>
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<tr>
<td>&gt;2 to ≤3</td>
<td>3968 3.1</td>
<td>133 0.9</td>
<td>61 1.0</td>
<td>8 1.2</td>
<td>19 0.5</td>
<td>50 2.3</td>
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<td>≥4</td>
<td>1547 1.2</td>
<td>101 0.7</td>
<td>45 0.7</td>
<td>9 1.3</td>
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<td>Cigarette smoking</td>
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<tr>
<td>Never smoked</td>
<td>63588 49.3</td>
<td>6871 48.5</td>
<td>3927 61.5</td>
<td>336 48.3</td>
<td>2942 71.5</td>
<td>1172 54.1</td>
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<td>Past smoker</td>
<td>55469 43.0</td>
<td>5418 38.2</td>
<td>1871 29.3</td>
<td>269 38.7</td>
<td>985 23.9</td>
<td>808 37.3</td>
<td></td>
<td></td>
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<tr>
<td>Current smoker</td>
<td>8436 6.5</td>
<td>1586 11.2</td>
<td>457 7.2</td>
<td>73 10.5</td>
<td>164 4.0</td>
<td>148 6.8</td>
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<tr>
<td>More than 30% of calories from fat?</td>
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<tr>
<td>Yes</td>
<td>85858 66.5</td>
<td>10060 71.0</td>
<td>4257 66.6</td>
<td>479 68.8</td>
<td>2480 60.3</td>
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<tr>
<td>Born in the United States?</td>
<td>68978 94.5</td>
<td>6782 96.7</td>
<td>1816 58.6</td>
<td>379 96.7</td>
<td>1873 72.6</td>
<td>968 78.8</td>
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<tr>
<td>Physical activity</td>
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<tr>
<td>No activity</td>
<td>18115 14.0</td>
<td>3217 22.7</td>
<td>1322 20.7</td>
<td>134 19.3</td>
<td>609 14.8</td>
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<tr>
<td>Some activity</td>
<td>48606 37.7</td>
<td>6114 43.2</td>
<td>2736 42.8</td>
<td>310 44.5</td>
<td>1809 44.0</td>
<td>898 41.5</td>
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<tr>
<td>2–3 episodes of moderate/strenuous activity</td>
<td>22464 17.4</td>
<td>2011 14.2</td>
<td>829 13.0</td>
<td>82 11.8</td>
<td>695 16.9</td>
<td>370 17.1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(exceeding 20 min)/wk</td>
<td>≥4 episodes of</td>
<td></td>
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</tr>
<tr>
<td>moderate/strenuous activity (exceeding 20 min)/wk</td>
<td>33444 25.9</td>
<td>2310 16.3</td>
<td>1124 17.6</td>
<td>147 21.1</td>
<td>945 23.0</td>
<td>470 21.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at menopause, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>26435 20.5</td>
<td>4203 29.7</td>
<td>1465 22.9</td>
<td>227 32.6</td>
<td>711 17.3</td>
<td>514 23.7</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>45 to 54</td>
<td>78878 61.1</td>
<td>6973 49.2</td>
<td>3539 55.4</td>
<td>333 47.8</td>
<td>2681 65.2</td>
<td>1233 57.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;54</td>
<td>17032 13.2</td>
<td>1608 11.4</td>
<td>653 10.2</td>
<td>60 8.6</td>
<td>554 13.5</td>
<td>268 12.4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P values are from chi-square test of association.
were younger and had higher BMI than white or Asian/Pacific Islander women or women with unknown ethnicity/race. More than 50% of African American women were obese (defined as BMI $\geq$ 30 kg/m$^2$), and over 10% of African American women had BMI of 40 kg/m$^2$ or higher (data not shown). Women of every minority group were less likely to drink alcohol than white women. White women and women in the Asian/Pacific Islander group had a higher age at first birth than women in the other groups. Except for women in the Asian/Pacific Islander group, minority women were less likely than white women to have ever been on hormone therapy or to have a college or higher degree.

Although mammogram frequency was protocol defined for women in the clinical trial component of the WHI, mammogram frequency differed across racial/ethnic groups, both among the population as a whole and for participants in the observational study and in the clinical trials (Table 2, $P<.001$). White women had a higher rate of mammography than women of any other racial/ethnic group.

During the follow-up period (median of 6.3 years), 3938 new invasive breast cancers were identified in 3455 white, 242 African American, 103 Hispanic, 88 Asian/Pacific Islander, and 11 American Indian/Native Alaskan women and in 39 women of unknown race/ethnicity. Age and cohort (i.e., clinical trial versus observational study)—stratified breast cancer hazard ratios varied statistically significantly by ethnicity. With white women as the referent group, hazard ratios were statistically significantly lower than 1 among Asian/Pacific Islanders, African Americans, and Hispanics (Fig. 1, $P<.001$ for global test of whether any of the estimated hazard ratios were equal to unity). The adjusted hazard ratio in American Indians/Native Alaskans relative to whites was also lower than 1 but not statistically significantly so, possibly because of the small numbers of cases.

After adjusting for the risk factors in the Gail model (age; number of first-degree relatives with breast cancer; ages at menarche, first birth, and menopause; and prior breast biopsy for benign breast disease), all hazard ratios comparing minority groups with whites were attenuated. Although all hazard ratios remained below 1, indicating lower risk in minority women (global test of race/ethnicity, $P = .05$), the results were statistically significant only for African American women ($P = .05$). The results were close to statistical significance for Hispanic women ($P = .07$).

In the final model, adjustment for additional risk factors and covariates, including mammography, further moderated the differences between minorities and white women. Hazard

### Table 2. Average rate of mammograms per year during follow-up by race/ethnicity and study component*

<table>
<thead>
<tr>
<th>Study component</th>
<th>White [Mean (SD)]</th>
<th>African American [Mean (SD)]</th>
<th>Hispanic [Mean (SD)]</th>
<th>Asian/Pacific Islander [Mean (SD)]</th>
<th>Unknown [Mean (SD)]</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.76 (0.24)</td>
<td>0.70 (0.25)</td>
<td>0.68 (0.27)</td>
<td>0.72 (0.24)</td>
<td>0.74 (0.25)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CT</td>
<td>0.77 (0.23)</td>
<td>0.73 (0.25)</td>
<td>0.71 (0.28)</td>
<td>0.76 (0.23)</td>
<td>0.74 (0.25)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>OS</td>
<td>0.76 (0.24)</td>
<td>0.67 (0.26)</td>
<td>0.65 (0.26)</td>
<td>0.74 (0.25)</td>
<td>0.70 (0.26)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*CT = clinical trial; OS = observational study; SD = standard deviation. $P$ value for differences among race/ethnicities based upon an F test from an AVOVA model.

![Figure 1](http://jnci.oxfordjournals.org/)
ratios for both Hispanics and Asian/Pacific Islanders (0.98 and 0.94, respectively) were statistically indistinguishable from 1. Only African American women had a statistically significantly ($P = .006$) lower breast cancer risk than white women when the additional risk factors were included (hazard ratio relative to white women = 0.75, 95% confidence interval [CI] = 0.61 to 0.92).

When the influence of age, family history, reproductive history, higher education, and alcohol intake on breast cancer risk was examined across ethnicity/race in expanded Cox models, no statistically significant interactions between race/ethnicity and these breast cancer risk factors on breast cancer incidence were seen (data not shown). Further, no evidence of interaction between race/ethnicity and study component (i.e., observational study versus clinical trial) with respect to breast cancer incidence was found.

Tumor histology, size, and stage did not differ statistically significantly by race/ethnicity (Table 3). However, there were highly statistically significant ($P < .001$) differences in the distribution of hormone receptor status and tumor grade by race/ethnicity; the differences between white women and African American women were especially great. Consequently, we determined hazard ratios of these disease subtypes for African American women compared with those in white women. African American women had a lower incidence of both well-differentiated (HR = 0.52, 95% CI = 0.35 to 0.77) and moderately differentiated (HR = 0.59, 95% CI = 0.43 to 0.80) tumors than white women and a higher incidence of poorly differentiated tumors (HR = 1.36, 95% CI = 1.06 to 1.75). African American women also had lower incidences of ER-positive and PR-positive tumors than white women (HR = 0.72, 95% CI = 0.59 to 0.87 and HR = 0.63, 95% CI = 0.50 to 0.79, respectively) and a higher incidence of ER-negative tumors (HR = 1.54, 95% CI = 1.11 to 2.14). The incidence of PR-negative tumors was slightly higher in African American women than in white women (HR = 1.29, 95% CI = 1.00 to 1.67). African American women also had substantially higher rates of ER-negative cancers and high-grade cancers than women of the other racial/ethnic groups. For example, among African American women, 43% of breast cancers were poorly differentiated (grade 3), compared with 27% or less in women of all other ethnic/racial groups.

Because tumor grade and ER status independently influence breast cancer outcome (21), we also examined the joint distribution of these factors by race/ethnicity. Nearly one-third of all breast cancers in African American women were both high grade (poorly differentiated) and ER negative, a frequency substantially

### Table 3. Characteristics of invasive breast cancers by race/ethnicity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>White (N = 3455)</th>
<th>African American (N = 242)</th>
<th>Hispanic (N = 103)</th>
<th>American Indian/ Native Alaskan (N = 11)</th>
<th>Asian/Pacific Islander (N = 88)</th>
<th>Unknown (N = 39)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor size, cm, mean (SD)</strong></td>
<td>1.56 (1.28)</td>
<td>1.60 (1.27)</td>
<td>1.89 (1.74)</td>
<td>1.64 (0.96)</td>
<td>1.95 (0.77)</td>
<td>1.49 (1.09)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Tumor size, cm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.58</td>
</tr>
<tr>
<td>Missing/other†</td>
<td>971 28</td>
<td>85 35</td>
<td>35 34</td>
<td>5 46</td>
<td>26 30</td>
<td>11 28</td>
<td></td>
</tr>
<tr>
<td>≤0.5</td>
<td>238 7</td>
<td>18 7</td>
<td>4 4</td>
<td>0 0</td>
<td>7 8</td>
<td>2 5</td>
<td></td>
</tr>
<tr>
<td>&gt;0.5 – 1</td>
<td>731 21</td>
<td>32 13</td>
<td>16 16</td>
<td>1 9</td>
<td>21 24</td>
<td>10 26</td>
<td></td>
</tr>
<tr>
<td>&gt;1 – 2</td>
<td>1026 30</td>
<td>60 25</td>
<td>32 31</td>
<td>2 18</td>
<td>23 26</td>
<td>10 26</td>
<td></td>
</tr>
<tr>
<td>&gt;2 – 5</td>
<td>431 13</td>
<td>43 18</td>
<td>15 15</td>
<td>3 27</td>
<td>11 13</td>
<td>5 13</td>
<td></td>
</tr>
<tr>
<td>&gt;5</td>
<td>58 2</td>
<td>4 2</td>
<td>1 1</td>
<td>0 0</td>
<td>0 0</td>
<td>1 3</td>
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<tr>
<td><strong>SEER stage</strong></td>
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<tr>
<td>Missing</td>
<td>57 2</td>
<td>10 4</td>
<td>5 5</td>
<td>0 0</td>
<td>3 3</td>
<td>3 8</td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>2596 75</td>
<td>161 67</td>
<td>70 68</td>
<td>7 64</td>
<td>66 75</td>
<td>27 69</td>
<td></td>
</tr>
<tr>
<td>Regional</td>
<td>770 22</td>
<td>68 28</td>
<td>28 27</td>
<td>4 36</td>
<td>19 22</td>
<td>9 23</td>
<td></td>
</tr>
<tr>
<td>Distant</td>
<td>32 1</td>
<td>3 1</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
<td>0 0</td>
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<td><strong>Histology</strong></td>
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<td></td>
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<td></td>
<td></td>
<td>0.11</td>
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<tr>
<td>Missing/Other†</td>
<td>321 9</td>
<td>24 10</td>
<td>8 8</td>
<td>1 9</td>
<td>8 9</td>
<td>1 3</td>
<td></td>
</tr>
<tr>
<td>Ductal</td>
<td>2172 63</td>
<td>164 68</td>
<td>74 72</td>
<td>9 81</td>
<td>67 76</td>
<td>33 85</td>
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<tr>
<td>Lobular</td>
<td>329 10</td>
<td>25 10</td>
<td>8 8</td>
<td>0 0</td>
<td>7 8</td>
<td>1 3</td>
<td></td>
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<tr>
<td>Ductal and lobular</td>
<td>490 14</td>
<td>23 10</td>
<td>11 11</td>
<td>1 9</td>
<td>3 3</td>
<td>2 5</td>
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</tr>
<tr>
<td>Tubular</td>
<td>143 4</td>
<td>6 3</td>
<td>2 2</td>
<td>2 0</td>
<td>3 3</td>
<td>2 5</td>
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<tr>
<td><strong>Morphology grade</strong></td>
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<td></td>
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<td>&lt;.001</td>
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<tr>
<td>Missing/unknown/not done</td>
<td>437 13</td>
<td>44 18</td>
<td>11 11</td>
<td>1 9</td>
<td>5 6</td>
<td>1 3</td>
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</tr>
<tr>
<td>Well differentiated</td>
<td>872 25</td>
<td>32 13</td>
<td>23 22</td>
<td>1 9</td>
<td>25 28</td>
<td>8 21</td>
<td></td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>1291 37</td>
<td>62 26</td>
<td>41 40</td>
<td>6 55</td>
<td>42 48</td>
<td>19 49</td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>855 25</td>
<td>104 43</td>
<td>28 27</td>
<td>3 27</td>
<td>16 18</td>
<td>11 28</td>
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<td><strong>Receptor status</strong></td>
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<tr>
<td>Missing/unknown/not done</td>
<td>363 11</td>
<td>35 14</td>
<td>17 17</td>
<td>1 9</td>
<td>5 6</td>
<td>3 8</td>
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<tr>
<td>Positive</td>
<td>2646 77</td>
<td>137 57</td>
<td>68 66</td>
<td>8 73</td>
<td>72 82</td>
<td>32 82</td>
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<tr>
<td>Negative</td>
<td>446 13</td>
<td>70 29</td>
<td>18 17</td>
<td>2 18</td>
<td>11 13</td>
<td>4 10</td>
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<td>Progesterone receptor</td>
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<td>&lt;.001</td>
</tr>
<tr>
<td>Missing/unknown/not done</td>
<td>424 12</td>
<td>44 18</td>
<td>23 22</td>
<td>1 9</td>
<td>8 9</td>
<td>3 8</td>
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<tr>
<td>Positive</td>
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<td>59 67</td>
<td>29 74</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>845 24</td>
<td>99 41</td>
<td>20 19</td>
<td>5 45</td>
<td>21 24</td>
<td>7 18</td>
<td></td>
</tr>
</tbody>
</table>

*P from chi-square test of association.
greater than that in women of other races/ethnicities (Table 4). In a multinomial logistic regression model that incorporated age, BMI, HT use, socioeconomic factors (health insurance status, income level, educational level), and ethnicity, BMI was only a modest, non–statistically significant ($P = .10$) predictor of high-grade plus ER-negative status, whereas ethnicity was a highly statistically significant ($P < .001$) predictor of this status. For example, the odds ratio for high-grade, ER-negative tumors in African American versus white women was 4.70 (95% CI = 3.12 to 7.09).

Finally, we compared mortality outcomes among white and African American racial/ethnic groups. After a median of 3.1 years following a breast cancer diagnosis, the cumulative mortality rate among African American women with breast cancer was 8.7% (21/242), whereas that among white women was 5.5% (191/3455). After adjusting for age, BMI, tumor stage, and study component, the risk of death after breast cancer in African American women remained statistically significantly elevated (HR = 1.79, 95% CI = 1.05 to 3.05).

**DISCUSSION**

In this large cohort of postmenopausal women, we found that all ethnic/racial groups had a lower age-adjusted breast cancer incidence than white women. However, the lower incidence in Hispanic, Asian/Pacific Islander, and American Indian/Native Alaskan women was mostly attenuated after adjustment for the distribution of other breast cancer risk factors. Dietary (22,23) and/or physical activity factors (24) may account for some of the remaining variability, but limitations in the precision of the tools that are available to estimate these factors (23) preclude definitive assessment.

Adjustment for breast cancer risk factors also explained some of the difference in breast cancer incidence between African American and white women. However, even in the final model, which adjusted for differential mammography screening rates, the breast cancer incidence was statistically significantly lower in African Americans than whites (HR = 0.75, $P = .006$). A potential factor mediating the lower breast cancer incidence in African American women is their mammographic breast density, which has been reported to be lower than that in white and Hispanic women (25).

The lower breast cancer incidence rates in racial/ethnic minority groups than in whites observed in the WHI cohort reflect the pattern previously reported in the general population (18). However, a comparison of age-adjusted rates from WHI with those for women in the SEER program indicates that breast cancer rates for all racial/ethnic subgroups except African Americans are somewhat higher for women in WHI than for women in SEER. That is, annualized age-adjusted incidence rates (in cases /10000 per year) for WHI and SEER, respectively, are white, 44 versus 41; African American, 29 versus 34; Hispanics, 31 versus 25; American Indians, 28 versus 16; and Asian/Pacific Islanders, 38 versus 25 (18). These modest differences may arise from higher educational status and greater access to health care, including screening mammography, for healthy women volunteering for placebo-controlled clinical prevention studies such as the WHI clinical trials.

Both SEER data and prior observational studies of associations between breast cancer incidence and ethnicity have been limited by the absence of comprehensive information on breast cancer screening. It is known that both Hispanic (26) and African American women (27,28) are less likely to undergo breast cancer screening than white women, but accurate assessment of this behavior in traditional case–control studies is difficult because retrospectively recalled frequency of mammography over long intervals has proven unreliable (29). In this WHI study, by contrast, information on mammography use was collected prospectively and incorporated in the final model. Even though the frequency of mammography was specified in the WHI protocol for the clinical trial participants (representing 58% of the study population), mammogram frequency still differed by ethnicity, with each racial/ethnic group having a somewhat lower rate of mammograms than white women.

The breast cancer risk model of Gail and colleagues is used widely, especially in the United States, to determine clinical prevention trial eligibility and in clinical practice as well (30,31). However, the Gail model was developed in a largely white population of women receiving regular mammograms (19) and has not been validated in other racial/ethnic groups (32). Indeed, the Gail model was recently adjusted to reflect a lower risk among Hispanic women (33,34). The results in this article suggest that further adjustments of the Gail model incorporating additional risk factors may provide more accurate risk calculation in minority populations.

Few studies have considered ethnicity as an integral component of comprehensive breast cancer risk assessment. In one multiethnic cohort, consideration of seven risk factors (ages at menarche and first birth, parity, age and type of menopause, weight, menopausal hormone therapy, and alcohol use) resulted in similar breast cancer risk in postmenopausal white, Hispanic, and African American women (35). However, that analysis did not incorporate several variables that are strongly related to breast cancer risk and that commonly vary by ethnicity (36), including breast cancer family history, prior benign breast disease, socioeconomic status, physical activity, and mammogram screening frequency. In the WHI population, a model incorporating only the

| Table 4. Grade and receptor status of breast cancers by race/ethnicity* |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Grade           | Estrogen receptor | White   | African American | Hispanic | Asian/Pacific Islander |
| Poorly differentiated | Negative  | 276     | 10.0             | 57       | 31.8             | 14               | 17.7             | 8               | 10.1             |
| Poorly differentiated | Positive | 495     | 17.8             | 35       | 19.6             | 7                | 8.9              | 8               | 10.1             |
| Moderate or well differentiated | Negative | 127     | 4.6              | 11       | 6.2              | 2                | 2.5              | 3               | 3.8              |
| Moderate or well differentiated | Positive | 1876    | 67.6             | 76       | 42.5             | 56               | 70.9             | 60              | 76.0             |
| All             | All            | 2774    | 100.0            | 179      | 100.0            | 79               | 100.0            | 79              | 100.0            |

*Includes only women with known estrogen receptor status and known grade. Women of American Indian/Alaskan Native, and unknown ethnicity/race were excluded because of sparse data.
same seven risk factors (data not shown) resulted in estimates of a slightly lower risk of breast cancer for African Americans than for whites (HR = 0.84, 95% CI = 0.73 to 0.98). That HR moved further away from unity in our final model, which included the full range of breast cancer risk factors and covariates (HR = 0.75, 95% CI = 0.61 to 0.92).

Despite the lower incidence of breast cancer among African American women than among white women, we found that, among women who developed breast cancer, African Americans had higher mortality than white women. Several factors have been suggested to contribute to the higher breast cancer mortality in African American women than in white women (7,37), including poorer socioeconomic status with reduced access to health care (38,39), a lower frequency of mammography with delayed diagnosis (27,28), and reduced chemotherapy dosage related to underlying neutropenia (40). However, a disparity in survival between white and African American women with breast cancer treated in the same health care systems (41,42) as well as in the same cancer clinical trial group (43) suggests that factors other than access to health care or mammography or treatment differences play a role in this process.

One such factor could be differences in rates of obesity and high-grade cancer. In the WHI population analyzed for this study, the rate of obesity (defined as BMI ≥ 30 kg/m²) among African American women (51%) was nearly twice that among white women (28%, P<0.001), and their rate of high-grade cancers was also much greater (43% vs. 25%, P<0.001). A previously identified association between BMI and high-grade cancers (44–46) therefore provides a potential explanation for at least some of the poor outcomes in African American women with breast cancer. In addition, the African American women in the WHI cohort were nearly five times likelier than the white women to have breast cancers that were both high grade and ER negative. The higher incidence of poor-prognosis cancers in African American women persisted even after adjustment for BMI and socioeconomic factors. However, obesity was only a modest (P = .10) predictor of unfavorable breast cancer grade and ER status compared with African American ethnicity, which was strongly (P<.001) associated with risk of high-grade, ER-negative cancers. Therefore, obesity does not fully explain the higher rate of poor-prognosis cancers in African American women.

It remains to be determined whether differences in unidentified environmental exposures, genetic makeup, or other factors lead to the higher frequency of high-grade, ER-negative cancers in African Americans. The gradient in frequency of high-grade, ER-negative breast cancers seen comparing native Africans in Nigeria (who have the highest frequency) to African Americans (who have an intermediate frequency) to whites (who have the lowest frequency) (46) is consistent with involvement of either environmental or genetic differences in this process. Gene expression assay studies have identified breast cancer subtypes representing biologically distinct disease entities (47). The high-grade, ER-negative cancers seen in African American women may represent the “basal-like subtype,” which has a poor prognosis and is receptor negative and commonly high grade (47,48). Comparative analyses of gene expression in breast cancers by race/ethnicity are needed to evaluate the possibility that basal-like breast tumors are more common in African American than in women of other racial/ethnic groups.

Several genetic factors have the potential to influence the different breast cancer characteristics of African Americans and whites. One is BP1, a homeobox-containing gene that is associated with ER-negative breast cancer (49) and breast cancer aggressiveness (50). BP1 is more frequently expressed in breast tumors from African American women than in white women (P = .04) (51). Further exploration of BP1 and other genetic factors (51–53) that differ by ethnicity could potentially lead to an explanation of the disproportionate development of poor-prognosis breast cancers in African American women.

Our study has several limitations. These include a small number of participants in some of the racial/ethnic subgroups, which limits the ability to make conclusions in these groups. In addition, we had no information on breast cancer therapy. Finally, the findings apply only to postmenopausal women.

The study also had a number of strengths. These include its prospective design; a large, ethnically diverse study population recruited from a relatively homogeneous socioeconomic background; detailed baseline assessment of a large range of breast cancer risk factors; effective follow-up for breast cancer outcome; regular assessment of mammography use; and central blinded adjudication of breast cancers via pathology report review and description of breast cancer histologic characteristics.

The results of this study indicate that differences in breast cancer incidence rates between most racial/ethnic groups can be largely explained by differences in risk factors except in African American women. The results also provide a unifying concept for the unfavorable breast cancer outcome seen in African American women despite a lower incidence. That is, breast cancers diagnosed in African American women are more commonly high-grade with negative ER status than breast cancers diagnosed in women of other racial/ethnic groups. The more common development of such poor-prognosis cancers in African American women contributes to their increased breast cancer mortality, independent of differential access to health care or mammography.

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organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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