Ethnicity and Breast Cancer: Factors Influencing Differences in Incidence and Outcome

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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)[1] 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

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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, 5238 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 progestin.

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, $r_y(t;z) = r_{0y}(t)\exp(zB_y)$, where y represents ethnicity, z represents a vector of known risk factors, and B_y 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, $\int_o^t r_{0y}(u)du$, 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 $r_{0y}(u)$ 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

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

	White (N = 129 037)		African American (N = 14 170)		Hispanic (N = 6388)		American Indian/Alaskan Native (N = 696)		Asian/Pacific Islander (N = 4114)		Unknown (N = 2165)		
Characteristic	N	%	N	%	N	%	N	%	N	%	N	%	*P*
Age at screening, mean (SD)	63.5 (7.2)		61.5 (7.1)		60.2 (6.8)		61.5 (7.5)		63.0 (7.5)		63.6 (7.4)		<.001
No. of 1st-degree relatives with breast cancer													
0	102 454	79.4	11 237	79.3	5309	83.1	527	75.7	3434	83.5	1671	77.2	<.001
1	16 479	12.8	1443	10.2	533	8.3	92	13.2	431	10.5	260	12.0	
≥2	1697	1.3	206	1.5	71	1.1	8	1.2	61	1.5	47	2.2	
No. of 1st-degree relatives with breast cancer before age 45													
0	117 134	90.8	12 479	88.1	5759	90.2	597	85.8	3801	92.4	1900	87.8	<.001
1	3354	2.6	378	2.7	145	2.3	29	4.2	120	2.9	74	3.4	
≥2	142	0.1	29	0.2	9	0.1	1	0.1	5	0.1	4	0.2	
Age at menarche, y													
<12	27 732	21.5	3384	23.9	1567	24.5	167	24.0	851	20.7	515	23.8	<.001
12–13	71 981	55.8	7108	50.2	3059	47.9	328	47.1	2123	51.6	1096	50.6	
≥14	28 867	22.4	3591	25.3	1709	26.8	195	28.0	1134	27.6	539	24.9	
Age at first birth, y													
Nulliparous	14 868	11.5	1905	13.4	696	10.9	51	7.3	609	14.8	258	11.9	<.001
<20	14 589	11.3	3765	26.6	1087	17.0	173	24.9	207	5.0	320	14.8	
20–24	50 972	39.5	3775	26.6	1866	29.2	230	33.1	1167	28.4	781	36.1	
25–29	28 698	22.2	1684	11.9	894	14.0	80	11.5	1158	28.2	350	16.2	
≥30	9460	7.3	804	5.7	450	7.0	45	6.5	518	12.6	166	7.7	
Benign breast disease													
No	94 981	73.6	10 800	76.2	4912	76.9	530	76.2	3331	81.0	1631	75.3	<.001
Yes, 1 biopsy	18 803	14.6	1967	13.9	678	10.6	93	13.4	528	12.8	313	14.5	
Yes, 2 biopsies	7870	6.1	744	5.3	304	4.8	34	4.9	184	4.5	134	6.2	
BMI, kg/m^2													
<25	47 222	36.6	2252	15.9	1571	24.6	165	23.7	2391	58.1	680	31.4	<.001
25–30	44 729	34.7	4552	32.1	2404	37.6	207	29.7	1255	30.5	762	35.2	
≥30	35 982	27.9	7223	51.0	2342	36.7	309	44.4	447	10.9	701	32.4	
Menopausal hormonal therapy usage status (at baseline)													
Never used	53 136	41.2	8418	59.4	3284	51.4	343	49.3	1569	38.1	995	46.0	<.001
Past user	20 235	15.7	2100	14.8	872	13.7	113	16.2	579	14.1	376	17.4	
Current user	55 568	43.1	3631	25.6	2222	34.8	240	34.5	1964	47.7	791	36.5	

(Table continues)

Table 1 (continued).

Characteristic	White (N = 129 037)		African American (N = 14 170)		Hispanic (N = 6388)		American Indian/Alaskan Native (N = 696)		Asian/Pacific Islander (N = 4114)		Unknown (N = 2165)		*P*
	N	%	N	%	N	%	N	%	N	%	N	%	
Educational level													
0–8 years	844	0.7	435	3.1	1159	18.1	51	7.3	76	1.9	47	2.2	<.001
Some high school	3642	2.8	1260	8.9	595	9.3	62	8.9	134	3.3	117	5.4	
High school diploma/GED	22 656	17.6	1950	13.8	1015	15.9	113	16.2	651	15.8	406	18.8	
School after high school	48 787	37.8	5454	38.5	2193	34.3	311	44.7	1427	34.7	865	40.0	
College degree or higher	52 265	40.5	4893	34.5	1309	20.5	151	21.7	1795	43.6	715	33.0	
Mammogram in last 2 years?													
Yes	105 894	82.1	10 727	75.7	4313	67.5	498	71.6	3323	80.8	1700	78.5	<.001
Mammogram ever?													
Yes	124 399	96.4	13 341	94.2	5703	89.3	640	92.0	3930	95.5	2065	95.4	<.001
No. of full-term pregnancies													
Nulliparous	14 838	11.5	1887	13.3	678	10.6	50	7.2	607	14.8	257	11.9	<.001
1	10 368	8.0	2107	14.9	537	8.4	81	11.6	375	9.1	218	10.1	
2	32 649	25.3	3196	22.6	1261	19.7	131	18.8	1179	28.7	494	22.8	
3	32 096	24.9	2539	17.9	1302	20.4	164	23.6	990	24.1	489	22.6	
4	20 121	15.6	1715	12.1	1012	15.8	104	14.9	527	12.8	347	16.0	
≥5	18 254	14.2	2582	18.2	1492	23.4	160	23.0	416	10.1	334	15.4	
Alcoholic drinks per day													
Nondrinker	49 145	38.1	9083	64.1	3646	57.1	382	54.9	2977	72.4	1086	50.2	<.001
≤1	62 783	48.7	4457	31.5	2422	37.9	261	37.5	1010	24.6	894	41.3	
>1 to ≤2	11 302	8.8	363	2.6	190	3.0	34	4.9	88	2.1	111	5.1	
>2 to ≤3	3968	3.1	133	0.9	61	1.0	8	1.2	19	0.5	50	2.3	
>3	1547	1.2	101	0.7	45	0.7	9	1.3	12	0.3	17	0.8	
Cigarette smoking													
Never smoked	63 588	49.3	6871	48.5	3927	61.5	336	48.3	2942	71.5	1172	54.1	<.001
Past smoker	55 469	43.0	5418	38.2	1871	29.3	269	38.7	985	23.9	808	37.3	
Current smoker	8436	6.5	1586	11.2	457	7.2	73	10.5	164	4.0	148	6.8	
More than 30% of calories from fat?													
Yes	85 858	66.5	10060	71.0	4257	66.6	479	68.8	2480	60.3	1383	63.9	<.001
Born in the United States?													
Yes	68 978	94.5	6782	96.7	1816	58.6	379	96.7	1873	72.6	968	78.8	<.001
Physical activity													
No activity	18115	14.0	3217	22.7	1322	20.7	134	19.3	609	14.8	360	16.6	<.001
Some activity	48 606	37.7	6114	43.2	2736	42.8	310	44.5	1809	44.0	898	41.5	
2–3 episodes of moderate/strenuous activity (exceeding 20 min)/wk	22 464	17.4	2011	14.2	829	13.0	82	11.8	695	16.9	370	17.1	
≥4 episodes of moderate/strenuous activity (exceeding 20 min)/wk	33 444	25.9	2310	16.3	1124	17.6	147	21.1	945	23.0	470	21.7	
Age at menopause, y													
<45	26 435	20.5	4203	29.7	1465	22.9	227	32.6	711	17.3	514	23.7	<.001
45 to 54	78 878	61.1	6973	49.2	3539	55.4	333	47.8	2681	65.2	1233	57.0	
>54	17 032	13.2	1608	11.4	653	10.2	60	8.6	554	13.5	268	12.4	
Oophorectomy/hysterectomy status													
Bilateral oophorectomy	24 844	19.3	3069	21.7	1093	17.1	150	21.6	793	19.3	435	20.1	
Hysterectomy, unknown oophorectomy	1981	1.5	812	5.7	168	2.6	34	4.9	75	1.8	67	3.1	
Hysterectomy, no oophorectomy	25 594	19.8	4026	28.4	1608	25.2	183	26.3	571	13.9	418	19.3	
No hysterectomy, no oophorectomy	76 208	59.1	6178	43.6	3458	54.1	319	45.8	2658	64.6	1231	56.9	

**P* values are from chi-square test of association.

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

Study component	White [Mean (SD)]	African American [Mean (SD)]	Hispanic [Mean (SD)]	American Indian/Native Alaskan [Mean (SD)]	Asian/Pacific Islander [Mean (SD)]	Unknown [Mean (SD)]	*P*
All	0.76 (0.24)	0.70 (0.25)	0.68 (0.27)	0.68 (0.27)	0.75 (0.24)	0.72 (0.25)	<.001
CT	0.77 (0.23)	0.73 (0.25)	0.71 (0.28)	0.71 (0.28)	0.76 (0.23)	0.74 (0.25)	<.001
OS	0.76 (0.24)	0.67 (0.26)	0.65 (0.26)	0.66 (0.26)	0.74 (0.25)	0.70 (0.26)	<.001

*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.

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 ≥ 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

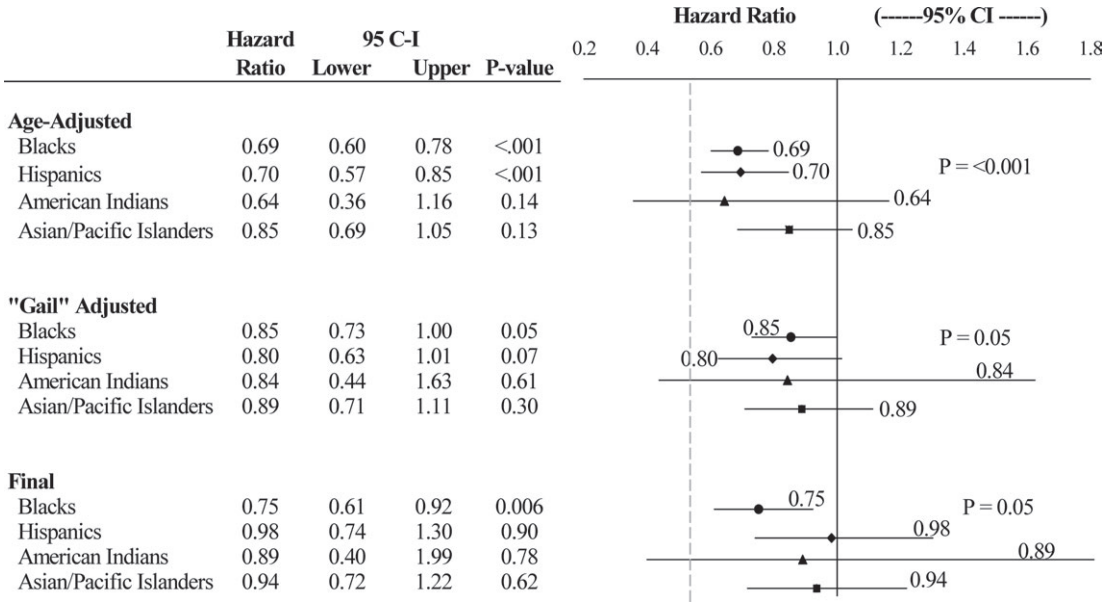

Fig. 1. Hazard ratios and *P* values of invasive breast cancer incidence by race/ethnicity after adjusting for breast cancer risk factors and other covariates. The age-adjusted model was adjusted for age only; the "Gail"-adjusted model was adjusted for age, number of first-degree relatives with breast cancer, age at menarche, age at first birth, and prior breast biopsy for benign disease; and the final model was adjusted for the covariates in Gail model plus education, BMI, physical activity, number of second-degree relatives with breast cancer, parity, hormone therapy (HT) use, prior contraceptive use, alcohol, smoking, dietary intake, HT×BMI interaction, and mammography (as a time-dependent covariate). *P* values on the right indicate a global test of whether breast cancer incidence differs by race/ethnicity; because of sparse data, tests did not include American Indians/Native Alaskans.

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

Characteristic	White (N = 3455)		African American (N = 242)		Hispanic (N = 103)		American Indian/Native Alaskan (N = 11)		Asian/Pacific Islander (N = 88)		Unknown (N = 39)		P*
	N	%	N	%	N	%	N	%	N	%	N	%	
Tumor size, cm, mean (SD)	1.56 (1.28)		1.60 (1.27)		1.89 (1.74)		1.64 (0.96)		1.95 (0.77)		1.49 (1.09)		0.12
Tumor size, cm													0.58
Missing/other†	971	28	85	35	35	34	5	46	26	30	11	28	
≤0.5	238	7	18	7	4	4	0	0	7	8	2	5	
>0.5 – 1	731	21	32	13	16	16	1	9	21	24	10	26	
>1 – 2	1026	30	60	25	32	31	2	18	23	26	10	26	
>2 – 5	431	13	43	18	15	15	3	27	11	13	5	13	
>5	58	2	4	2	1	1	0	0	0	0	1	3	
SEER stage													0.39
Missing	57	2	10	4	5	5	0	0	3	3	3	8	
Localized	2596	75	161	67	70	68	7	64	66	75	27	69	
Regional	770	22	68	28	28	27	4	36	19	22	9	23	
Distant	32	1	3	1	0	0	0	0	0	0	0	0	
Histology													0.11
Missing/Other†	321	9	24	10	8	8	1	9	8	9	1	3	
Ductal	2172	63	164	68	74	72	9	81	67	76	33	85	
Lobular	329	10	25	10	8	8	0	0	7	8	1	3	
Ductal and lobular	490	14	23	10	11	11	1	9	3	3	2	5	
Tubular	143	4	6	3	2	2	0	0	3	3	2	5	
Morphology grade													<.001
Missing/unknown/not done	437	13	44	18	11	11	1	9	5	6	1	3	
Well differentiated	872	25	32	13	23	22	1	9	25	28	8	21	
Moderately differentiated	1291	37	62	26	41	40	6	55	42	48	19	49	
Poorly differentiated	855	25	104	43	28	27	3	27	16	18	11	28	
Receptor status													
Estrogen receptor													<.001
Missing/unknown/not done	363	11	35	14	17	17	1	9	5	6	3	8	
Positive	2646	77	137	57	68	66	8	73	72	82	32	82	
Negative	446	13	70	29	18	17	2	18	11	13	4	10	
Progesterone receptor													<.001
Missing/unknown/not done	424	12	44	18	23	22	1	9	8	9	3	8	
Positive	2186	63	99	41	60	58	5	45	59	67	29	74	
Negative	845	24	99	41	20	19	5	45	21	24	7	18	

*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 /10 000 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*

Breast cancer characteristics		White		African American		Hispanic		Asian/Pacific Islander	
Grade	Estrogen receptor	N	Percent	N	Percent	N	Percent	N	Percent
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 $\geq$ 30 kg/m^2) among African American women (51%) was nearly twice that among white women (28%, $P<.001$), and their rate of high-grade cancers was also much greater (43% vs. 25%, $P<.001$). 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 of 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 of 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 difference 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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Notes

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit

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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