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Original Contribution

Breast Cancer Risk Factors Defined by Estrogen and Progesterone Receptor Status

The Multiethnic Cohort Study

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Prospective data on ethnic differences in hormone receptor-defined subtypes of breast cancer and their risk factor profiles are scarce. The authors examined the joint distributions of estrogen receptor (ER) and progesterone receptor (PR) status across 5 ethnic groups and the associations of established risk factors with ER/PR status in the Multiethnic Cohort Study (Hawaii and Los Angeles, California). During an average of 10.4 years of follow-up of 84,427 women between 1993–1996 and 2004/2005, 2,543 breast cancer cases with data on ER/PR status were identified: 1,672 estrogen receptor-positive (ER+)/progesterone receptor-positive (PR+); 303 ER+/progesterone receptor-negative (PR−); 77 estrogen receptor-negative (ER−)/PR+; and 491 ER−/PR−. ER/PR status varied significantly across racial/ethnic groups even within the same tumor stage (for localized tumors, $P < 0.0001$; for advanced tumors, $P = 0.01$). The highest fraction of ER−/PR− tumors was observed in African Americans (31%), followed by Latinas (25%), Whites (18%), Japanese (14%), and Native Hawaiians (14%). Associations differed between ER+/PR+ and ER−/PR− cases for postmenopausal obesity ($P = 0.02$), age at menarche ($P = 0.05$), age at first birth ($P = 0.04$), and postmenopausal hormone use ($P < 0.0001$). African Americans are more likely to be diagnosed with ER−/PR− tumors independently of stage at diagnosis, and there are disparate risk factor profiles across the ER/PR subtypes of breast cancer.

breast neoplasms; cohort studies; receptors, estrogen; receptors, progesterone; risk factors

Abbreviations: CI, confidence interval; ER, estrogen receptor; ER−, estrogen receptor-negative; ER+, estrogen receptor-positive; HR, hazard ratio; PR, progesterone receptor; PR−, progesterone receptor-negative; PR+, progesterone receptor-positive; SEER, Surveillance, Epidemiology, and End Results.

Estrogen receptor (ER) status and progesterone receptor (PR) status are biologic markers commonly evaluated in breast cancer to predict a patient's response to endocrine therapy and her prognosis. Women diagnosed with estrogen receptor-positive (ER+)/progesterone receptor-positive (PR+) tumors are more responsive to hormonal treatment and have a better prognosis than those diagnosed with estrogen receptor-negative (ER−)/progesterone receptor-negative (PR−) tumors. Several molecular subtypes based on gene-expression patterns in breast tumor tissue have been proposed, and these subtypes have distinct clinical outcomes (1–3). The basal-like subtypes and the subtypes expressing human epidermal growth factor receptor 2, which both are ER−/PR−, are more common among younger African Americans, and they have the poorest prognosis (1, 4).

Etiologic heterogeneity of hormone receptor-defined subtypes of breast cancer has been proposed, for several reasons. Age-specific incidence rates vary by hormone receptor status; incidence rates of ER− tumors do not increase after ages 50–54 years as do ER+ incidence rates (5). Racial/ethnic distributions also differ by hormone receptor status; ER−/PR− tumors account for approximately 15%–20% of

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breast cancer cases among White women but as much as 40% of cases in African-American women (6). Several studies have shown that known breast cancer risk factors closely associated with endogenous estrogen exposure are mainly associated with ER+ and/or PR+ tumors (7, 8). Finally, a recent large genetic association study showed differential associations between susceptibility loci identified from genome-wide scans and tumor subtypes defined by ER status (9), suggesting that hormone receptor-defined tumors are probably distinct at the germline level as well.

Investigators in several studies have demonstrated that African-American women are more often diagnosed with negative hormone receptor tumors than White women and have examined the associations of known breast cancer risk factors (7, 8) with ER and/or PR status. However, data on other racial/ethnic groups (Latinas, Japanese, and Native Hawaiians) and risk factor data from prospective cohort studies in which ER and PR status are considered jointly are scarce (10–16). Here we examined the distributions of ER/PR subtypes across 5 racial/ethnic groups (African Americans, Japanese Americans, Latinas, Native Hawaiians, and Whites) and the associations of established breast cancer risk factors with joint ER/PR status, using data from a large prospective multiethnic cohort study.

MATERIALS AND METHODS

Study population

The Multiethnic Cohort Study is a prospective cohort study designed to examine the association of diet, lifestyle, and genetic factors with incidence of cancer and other chronic diseases. Details on the study design, response rates, and baseline characteristics have been given elsewhere (17). Briefly, recruitment of the cohort began in 1993 and was completed in 1996. Potential participants were identified through driver's license files, voter registration lists, and Health Care Financing Administration data files. The cohort consists of more than 215,000 men and women (aged 45–75 years at cohort creation in 1993) living in Hawaii and California (mainly Los Angeles County) and comprises largely 5 self-reported racial/ethnic populations: African Americans, Japanese Americans, Latinos, Native Hawaiians, and Whites. Each participant completed a self-administered mailed baseline questionnaire that included questions on diet, demographic factors, anthropometric measures, other lifestyle factors, history of various medical conditions, family history of cancer, and, for women, menstrual and reproductive history and exogenous hormone use. The institutional review boards at the University of Hawaii and the University of Southern California approved the study protocol.

Inclusion and exclusion criteria

Only women from the 5 main racial/ethnic groups who were free of breast, uterine, and ovarian cancer at the time of the baseline questionnaire were included in the current analysis ($n = 98{,}393$). Women were excluded from the present analysis if they had missing data for any of the following variables: body mass index (weight (kg)/height $(m)^2$), age at menarche, age at first full-term pregnancy, number of children, type of menopause, use of hormone therapy, and alcohol consumption ($n = 13{,}966$). After all exclusions, 84,427 women comprised the final study cohort. Excluded subjects were similar to those who remained in the analyses with respect to age and distribution of breast cancer risk factors.

Follow-up and case identification

Follow-up began when participants completed the baseline questionnaire and continued to the first of the following endpoints: 1) diagnosis of invasive breast cancer (*International Classification of Diseases for Oncology* code C50), 2) death, or 3) the end of follow-up (December 31, 2004, for Hawaii and December 31, 2005, for Los Angeles). Incident cases of breast cancer were identified by record linkage to the Hawaii Tumor Registry, the Los Angeles County Cancer Surveillance Program, and the California State Cancer Registry. All of these tumor registries participate in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Information on ER and PR status (positive/negative) was obtained from these tumor registries. Deaths occurring within the cohort were determined by annual linkage to state death certificate files in California and Hawaii and periodic linkage to the National Death Index. Death information was complete through December 31, 2005.

Statistical analysis

In the case-only analysis, differences in the distribution of ER/PR status across categories of tumor stage and race/ethnicity were tested using χ^2 tests. In the cohort analysis, hazard ratios and corresponding 95% confidence intervals associated with breast cancer risk factors were estimated using log-linear (Cox) proportional hazards models. The underlying time variable in the analysis was time from the date of enrollment to the date of breast cancer diagnosis, death, or censoring. The Cox model for each ER/PR subtype included stratification on age at recruitment (in 1-year age groups), year of recruitment (single years), race/ethnicity (5 groups), menopause status and type (premenopausal, natural menopause, bilateral oophorectomy, or simple hysterectomy) at recruitment, and study center (Hawaii/Los Angeles). The multivariate hazard ratios for each ER/PR subtype were calculated for the following risk factors: body mass index (<25, 25–<30, or ≥ 30), age at natural menopause (<45, 45–<50, 50–<55, or ≥ 55 years), age at menarche (≤ 12, 13–14, or ≥ 15 years), age at first full-term pregnancy (nulliparous or ≤ 20, >20–<31, or ≥ 31 years), number of children (1, 2–3, or ≥ 4), alcohol consumption (none, <2 drinks/day (<24 ethanol g/day), or ≥ 2 drinks/day (≥ 24 ethanol g/day)), postmenopausal hormone therapy use and duration (never use, past use, current use of estrogen therapy, or current use of estrogen-progestin therapy), and family history of breast cancer in a first-degree relative (no/yes). Duration of hormone therapy was calculated using methods previously described (18).

Tests for trend for body mass index and alcohol intake were conducted by fitting the median values of each category as a continuous term in the multivariate models; for categorical variables, trend tests were conducted by treating each category as a continuous term (0, 1, 2, ...). All trend tests were based on the Wald statistic. Differences in risk factor associations between ER+/PR+ and ER−/PR− groups were compared in an overall model using competing risk techniques, where ER/PR status was a different event (19). A Wald test was used to compare the parameters between ER/PR status strata. The proportional hazards assumption was tested by examining the Kaplan-Meier curves and assessing the Schoenfeld residuals; no major violations were observed. All *P* values reported are 2-sided. Statistical analyses were performed in SAS, version 9.1 (SAS Institute Inc., Cary, North Carolina), and Stata, version 10 (Stata Corporation, College Station, Texas).

RESULTS

A total of 3,270 incident cases of breast cancer were identified during an average of 10.4 years of follow-up. The baseline characteristics of the whole cohort and breast cancer cases and the age-adjusted incidence rates of breast cancer are shown in Table 1. Japanese Americans comprised the largest group, with 28% of the population, followed by Whites (26%), Latinas (21%), African Americans (19%), and Native Hawaiians (7%). Breast cancer incidence rates were highest in Native Hawaiians, followed by Japanese Americans, Whites, African Americans, and Latinas. Higher incidences of breast cancer were observed in women with a body mass index greater than 30, an earlier age at menarche, a later age at first birth, fewer children, a first-degree family history of breast cancer, consumption of at least 2 alcoholic drinks per day, and current use of estrogen-progestin therapy.

Overall, we had information on joint ER/PR status for 2,543 (78%) breast cancer cases. Cases with an unknown ER/PR status ($n = 727$; 22%) were similar to those with a known ER/PR status with respect to breast cancer risk factors (see Appendix Table).

Among cases with a known hormone receptor status, 1,672 (66%) were ER+/PR+, 303 (12%) were ER+/PR−, 77 (3%) were ER−/PR+, and 491 (19%) were ER−/PR− (Table 2). The average ages at diagnosis were similar in the 3 major hormone receptor groups ER+/PR+, ER+/PR−, and ER−/PR−, but the average age at diagnosis was younger in ER−/PR+ cases. ER/PR status varied significantly by tumor stage ($P = 0.0003$). Tumors in cases with advanced disease were more often ER−/PR− than those in cases with localized disease (24% vs. 17%). The distribution of ER/PR subtypes varied significantly across racial/ethnic groups ($P < 0.0001$); the proportion of ER−/PR− tumors was higher in African Americans (31%) and Latinas (25%) than in Whites (18%), Japanese Americans (14%), and Native Hawaiians (14%). Even among cases with the same tumor stage, there was significant variation across racial/ethnic groups (for localized tumors, $P < 0.0001$; for advanced tumors, $P = 0.01$). After stratification on tumor stage, African Americans continued to have a significantly higher proportion of ER−/PR− tumors than Whites (31% vs. 16% ($P < 0.0001$) for localized tumors and 32% vs. 20% ($P = 0.01$) for advanced tumors). Although Latinas also had a higher proportion of ER−/PR− tumors (22% of localized tumors and 30% of advanced tumors) than Whites, the differences were not statistically significant.

Table 3 shows the association between known risk factors and breast cancer by joint ER/PR status. Because the number of ER−/PR+ cases ($n = 77$) was too small for meaningful interpretations, we do not present those results in the table. Body mass index was positively associated with the risk of ER+/PR+ tumors (*P*-trend < 0.001). The risk of ER+/PR+ tumors was increased in overweight women (body mass index 25–<30) (hazard ratio (HR) = 1.27, 95% confidence interval (CI): 1.13, 1.43) and obese women (body mass index ≥ 30) (HR = 1.52, 95% CI: 1.32, 1.75) relative to normal-weight women (body mass index < 25). Body mass index was not associated with ER+/PR− or ER−/PR− tumors. When the analysis was restricted to women with natural menopause or bilateral oophorectomy, similar results were observed. The test for interaction revealed a statistically significant difference between ER+/PR+ and ER−/PR− subtypes for postmenopausal obesity ($P = 0.02$).

Late age at menarche was significantly associated with reduced risk of ER+/PR+ tumors (*P*-trend = 0.03). Compared with women with an early age at menarche (age $\leq$12 years), there was an 18% reduction in risk of ER+/PR+ tumors for women who experienced menarche at age $\geq$15 years (HR = 0.82, 95% CI: 0.69, 0.97). It appeared that later age at menarche also lowered the risk of ER+/PR− tumors, but the trend did not reach statistical significance (*P*-trend = 0.13). Age at menarche was not associated with ER−/PR− tumors. The test for interaction between ER+/PR+ and ER−/PR− subtypes for age at menarche was borderline-significant ($P = 0.05$).

Among a subset of women with natural menopause ($n = 44{,}717$), later age at menopause was associated with an increased risk of ER+/PR+ tumors (*P*-trend = 0.001). Compared with women with early menopause (age <45 years), those who underwent menopause after ages 50 and 55 years had 31% (95% CI: 1.06, 1.63) and 52% (95% CI: 1.17, 1.98) higher risks of ER+/PR+ tumors, respectively. Late age at natural menopause also seemed to increase the risk of ER+/PR− tumors, but the trend was not significant (*P*-trend = 0.10). No significant association was observed between age at natural menopause and ER−/PR− tumors.

Among parous women, late age at first birth was associated with a higher risk of ER+/PR+ tumors (*P*-trend $<$ 0.001). Women who had their first child at ages 26–30 years and >30 years had 40% (HR = 1.40, 95% CI: 1.18, 1.66) and 52% (HR = 1.52, 95% CI: 1.22, 1.90) higher risks of ER+/PR+ tumors, respectively, than women who had their first child before age 21 years. Late age at first birth was also associated with an increased risk of ER+/PR− tumors (*P*-trend = 0.03), especially among women who had their first child after age 30 years (HR = 1.68, 95% CI: 1.01,

Table 1. Baseline Characteristics of the Cohort and of Breast Cancer Cases, Multiethnic Cohort Study, 1993–1996 to 2004/2005

Characteristic	Entire Cohort (n = 84,427)	Cases (n = 3,270)	Breast Cancer Incidence Rate[a]
Mean age at cohort entry, years	59.1 (8.8)[b]	60.1 (8.5)	
Race/ethnicity, %			
African-American	18.6	19.1	336.2
Japanese-American	28.1	30.7	418.8
Latina	20.5	14.7	233.7
Native Hawaiian	7.4	8.8	506.4
White	25.5	26.6	359.2
Body mass index[c], %			
<25	47.7	45.5	351.2
25–<30	31.0	32.2	347.5
≥30	21.3	22.3	363.0
Age (years) at menarche, %			
≤12	49.9	51.9	369.6
13–14	38.2	37.5	348.5
≥15	11.8	10.6	292.0
Age (years) at first livebirth, %			
Nulliparous	13.0	15.8	440.3
≤20	28.9	23.1	269.1
21–25	35.1	34.3	342.2
26–30	16.3	18.5	426.5
≥31	6.7	8.3	474.4
Parity[d], %			
1	13.0	14.5	407.5
2–3	51.3	55.1	368.8
≥4	35.6	30.4	272.1
Type of menopause, %			
None (premenopausal)	15.2	13.0	307.9
Natural menopause	53.0	57.0	366.2
Oophorectomy	14.9	13.4	285.1
Hysterectomy	16.9	16.7	341.5
Postmenopausal hormone therapy, %			
Never use	52.4	45.4	316.3
Former use	16.8	16.0	299.4
Current use of estrogen therapy	14.1	14.2	329.3
Current use of estrogen-progestin therapy	16.8	24.4	500.6
Alcohol intake (drinks/day), %			
0	60.8	59.0	343.8
<2	33.9	33.7	349.7
≥2	5.3	7.3	487.7
First-degree family history of breast cancer, %			
No	88.9	82.7	330.2
Yes	11.1	17.3	546.2

[a] Incidence rate per 100,000 women; age-adjusted to the 1970 US standard population.
[b] Numbers in parentheses, standard deviation.
[c] Weight (kg)/height $(m)^2$.
[d] Among parous women.

Table 2. Age at Diagnosis and Hormone Receptor Status Among Breast Cancer Cases, by Race/Ethnicity and Disease Stage, Multiethnic Cohort Study, 1993–1996 to 2004/2005

	ER+/PR+		ER+/PR−		ER−/PR+		ER−/PR−		Total		χ^2 (df)	*P* Value
Mean age at diagnosis, years	65.6 (8.7)[a]		66.3 (8.8)		60.5 (9.0)		64.4 (9.1)		65.3 (8.9)			
	No.	Row %	No.	Row %	No.	Row %	No.	Row %	No.	Row %		
No. and % of cases	1,672	65.8	303	11.9	77	3.0	491	19.3	2,543	100.0		
Tumor stage											18.6 (3)[b]	0.0003[b]
Localized	1,192	68.3	193	11.1	58	3.3	303	17.4	1,746	100.0		
Advanced[c]	426	60.3	95	13.5	18	2.6	167	23.7	706	100.0		
Unknown	54	59.3	15	16.5	1	1.1	21	23.1	91	100.0		
Race/ethnicity											87.3 (12)	<0.0001
African-American	216	51.4	51	12.1	23	5.5	130	30.9	420	100.0		
Japanese-American	592	70.5	103	12.3	25	3.0	120	14.3	840	100.0		
Latina	203	60.1	44	13.0	8	2.4	83	24.6	338	100.0		
Native Hawaiian	184	75.4	18	7.4	7	2.9	35	14.3	244	100.0		
White	477	68.1	87	12.4	14	2.0	123	17.6	701	100.0		
Localized tumors											63.9 (12)	<0.0001
African-American	128	53.8	20	8.4	17	7.1	73	30.7	238	100.0		
Japanese-American	465	72.3	73	11.4	20	3.1	85	13.2	643	100.0		
Latina	133	61.9	29	13.5	6	2.8	47	21.9	215	100.0		
Native Hawaiian	126	75.9	15	9.0	4	2.4	21	12.7	166	100.0		
White	340	70.3	56	11.6	11	2.3	77	15.9	484	100.0		
Advanced tumors											25.9 (12)	0.01
African-American	74	48.4	24	15.7	6	3.9	49	32.0	153	100.0		
Japanese-American	116	63.0	28	15.2	5	2.7	35	19.0	184	100.0		
Latina	56	54.4	14	13.6	2	1.9	31	30.1	103	100.0		
Native Hawaiian	57	75.0	3	3.9	2	2.6	14	18.4	76	100.0		
White	123	64.7	26	13.7	3	1.6	38	20.0	190	100.0		

Abbreviations: ER−, estrogen receptor-negative; ER+, estrogen receptor-positive; PR−, progesterone receptor-negative; PR+, progesterone receptor-positive.

[a] Numbers in parentheses, standard deviation.

[b] Tumors with an unknown stage ($n = 91$) were excluded.

[c] Regional and distant cancer.

2.80). Late age at first birth also appeared to increase the risk of ER−/PR− tumors, but the observed association and the weaker trend were not statistically significant. The test for interaction between ER+/PR+ and ER−/PR− subtypes for age at first birth was borderline-significant ($P = 0.04$).

Having a greater number of children was protective against ER+/PR+ tumors (P-trend < 0.001). Compared with women with 1 child, those with 2–3 children and ≥4 children had 9% (HR = 0.91, 95% CI: 0.78, 1.08) and 27% (HR = 0.73, 95% CI: 0.60, 0.88) reductions in the risk of an ER+/PR+ tumor, respectively. Increasing parity did not lower the risk of developing ER+/PR− or ER−/PR− tumors.

In postmenopausal women, current use of estrogen-progestin therapy was significantly associated with ER+/PR+ tumors (HR = 2.28, 95% CI: 1.97, 2.64), and the risk was estimated to increase 45% per 5 years of use (95% CI: 1.35, 1.55). Current use of estrogen-progestin therapy was also associated with ER+/PR− tumors, but the hazard ratio was much lower (HR = 1.63, 95% CI: 1.15, 2.33). Current use of estrogen therapy was associated with ER+/PR+ tumors (HR = 1.40, 95% CI: 1.11, 1.77), and the risk associated with 5 years of current estrogen therapy use was 1.13 (95% CI: 1.05, 1.22) for ER+/PR+. Neither estrogen-progestin therapy nor estrogen therapy was significantly associated with ER−/PR− tumors. The test for interaction revealed a significant difference between ER+/PR+ and ER−/PR− subtypes for postmenopausal hormone use ($P < 0.0001$).

Women who consumed 2 or more alcoholic drinks per day had elevated risks of tumors of all ER/PR subtypes, with the strongest association being observed for ER−/PR− tumors; compared with nondrinkers, these women had hazard ratios of 1.40 (95% CI: 1.14, 1.72) for ER+/PR+ tumors, 1.42 (95% CI: 0.85, 2.36) for ER+/PR− tumors, and 1.71 (95% CI: 1.19, 2.46) for ER−/PR− tumors. A first-degree family history of breast cancer was also associated with increased

Table 3. Associations Between Selected Risk Factors and Breast Cancer, by Hormone Receptor Status, Multiethnic Cohort Study, 1993–1996 to 2004/2005

	ER+/PR+ (n = 1,672)			ER+/PR− (n = 303)			ER−/PR− (n = 491)			P for Interaction[b]
	No. of Cases	RR[a]	95% CI	No. of Cases	RR[a]	95% CI	No. of Cases	RR[a]	95% CI	
Body mass index[c]										0.08
<25	775	1.00	Referent	153	1.00	Referent	235	1.00	Referent	
25–<30	527	1.27	1.13, 1.43	104	1.22	0.93, 1.60	161	0.98	0.79, 1.21	
≥30	370	1.52	1.32, 1.75	46	0.90	0.63, 1.30	95	0.79	0.60, 1.03	
P for trend			<0.001			0.75			0.07	
Body mass index among postmenopausal women[d]										0.02
<25	568	1.00	Referent	112	1.00	Referent	165	1.00	Referent	
25–<30	370	1.27	1.10, 1.46	74	1.30	0.95, 1.79	109	1.00	0.77, 1.30	
≥30	244	1.53	1.29, 1.81	31	0.98	0.63, 1.52	53	0.69	0.49, 0.98	
P for trend			<0.001			0.82			0.04	
Age at menarche, years										0.05
≤12	879	1.00	Referent	153	1.00	Referent	237	1.00	Referent	
13–14	628	0.95	0.85, 1.06	120	0.92	0.71, 1.18	190	1.07	0.88, 1.30	
≥15	165	0.82	0.69, 0.97	30	0.74	0.49, 1.11	64	1.18	0.88, 1.57	
P for trend			0.03			0.13			0.25	
Age at natural menopause, years										0.89
<45	120	1.00	Referent	23	1.00	Referent	37	1.00	Referent	
45–49	279	1.15	0.92, 1.44	51	1.09	0.65, 1.84	84	1.09	0.73, 1.63	
50–54	434	1.31	1.06, 1.63	76	1.18	0.71, 1.96	106	0.97	0.65, 1.45	
≥55	131	1.52	1.17, 1.98	28	1.66	0.91, 3.01	33	1.17	0.71, 1.93	
P for trend			0.001			0.10			0.81	
Age at first livebirth, years										0.04
Nulliparous	301	1.54	1.23, 1.92	38	1.31	0.75, 2.29	61	1.15	0.75, 1.76	
≤20	345	1.00	Referent	66	1.00	Referent	132	1.00	Referent	
21–25	558	1.16	1.00, 1.34	114	1.29	0.92, 1.79	185	1.22	0.96, 1.56	
26–30	330	1.40	1.18, 1.66	58	1.32	0.87, 1.98	77	1.16	0.84, 1.58	
≥31	138	1.52	1.22, 1.90	27	1.68	1.01, 2.80	36	1.32	0.87, 1.99	
P for trend[e]			<0.001			0.03			0.13	

Table continues

risk of breast cancer independently of ER/PR status, with hazard ratios ranging from 1.63 to 1.91.

DISCUSSION

Using data from the Multiethnic Cohort Study, we have shown that 1) ER/PR status in breast cancer cases varies across racial/ethnic groups, 2) ER−/PR− tumors are most common in African-American women, and 3) risk factor profiles differ across the ER/PR subtypes. Obesity and menstrual/reproductive factors, including use of hormone therapy, are associated mainly with ER+/PR+ breast cancers, while alcohol consumption and a family history of breast cancer are similarly associated with ER+/PR+ and ER−/PR− cancers.

In the Multiethnic Cohort Study, African Americans had the highest age-adjusted rate of mortality from breast cancer (82/100,000 women), followed by Native Hawaiians (73/100,000), Whites (67/100,000), Latinas (52/100,000), and Japanese Americans (41/100,000). These rates were based on 860 breast cancer deaths occurring within the cohort through December 31, 2005, and were age-adjusted to the 1970 US standard population. ER/PR status has been associated with breast cancer mortality independently of various demographic factors and clinical tumor characteristics (20). Previous studies (and now ours) have demonstrated that African-American women are more often diagnosed with hormone receptor-negative breast cancers than White women (6). Furthermore, we found that among women with tumors diagnosed at a localized stage, African Americans continued to have a high proportion of ER−/PR− tumors

Table 3. Continued

	ER+/PR+ (n = 1,672)			ER+/PR− (n = 303)			ER−/PR− (n = 491)			P for Interaction[b]
	No. of Cases	RR[a]	95% CI	No. of Cases	RR[a]	95% CI	No. of Cases	RR[a]	95% CI	
Parity[e]										0.17
1	208	1.00	Referent	35	1.00	Referent	57	1.00	Referent	
2–3	777	0.91	0.78, 1.08	153	1.10	0.74, 1.64	227	1.06	0.78, 1.45	
≥4	386	0.73	0.60, 0.88	77	0.98	0.62, 1.54	146	1.07	0.76, 1.51	
P for trend			<0.001			0.73			0.80	
Postmenopausal hormone therapy[d]										<0.0001
Never use	393	1.00	Referent	80	1.00	Referent	142	1.00	Referent	
Former use	205	1.25	1.05, 1.49	40	1.29	0.87, 1.91	65	1.11	0.81, 1.51	
Current use of estrogen therapy	133	1.40	1.11, 1.77	33	1.88	1.12, 3.14	44	1.21	0.79, 1.85	
Current use of estrogen-progestin therapy	451	2.28	1.97, 2.64	64	1.63	1.15, 2.33	76	1.11	0.82, 1.51	
Alcohol intake, drinks/day										0.07
0	997	1.00	Referent	172	1.00	Referent	267	1.00	Referent	
<2	551	1.03	0.92, 1.15	112	1.17	0.91, 1.51	185	1.21	0.99, 1.48	
≥2	124	1.40	1.14, 1.72	19	1.42	0.85, 2.36	39	1.71	1.19, 2.46	
P for trend			0.001			0.22			0.006	
Family history of breast cancer										0.47
No	1,377	1.00	Referent	248	1.00	Referent	398	1.00	Referent	
Yes	295	1.63	1.43, 1.86	55	1.72	1.27, 2.34	93	1.91	1.51, 2.43	

Abbreviations: CI, confidence interval; ER−, estrogen receptor-negative; ER+, estrogen receptor-positive; PR−, progesterone receptor-negative; PR+, progesterone receptor-positive; RR, relative risk.

[a] Results were stratified on age at recruitment, year of recruitment, race/ethnicity, type of menopause, and study center and were mutually adjusted for age at menarche, age at first birth, number of children, body mass index, alcohol intake, duration of hormone therapy, and family history of breast cancer.

[b] Interaction between ER+/PR+ and ER−/PR− subtypes as assessed using Wald statistics.

[c] Weight (kg)/height $(m)^2$.

[d] Women with natural menopause or bilateral oophorectomy.

[e] Among parous women.

compared with other racial/ethnic groups. The high prevalence of hormone receptor-negative tumors in African-American women may contribute to their high breast cancer mortality. Latinas have higher proportions of ER−/PR− tumors relative to Whites regardless of tumor stage, though not as high as those of African Americans. However, Latinas in our cohort had the lowest overall age-adjusted incidence rate and had mortality rates that were among the lowest. Our results suggest that Latinas may share some of the germline-related risk of African Americans. Future studies in these 2 populations should yield important insights into the etiology of the ER−/PR− subtype of breast cancer.

Japanese-American women in our cohort had a higher age-adjusted incidence rate of breast cancer than White women, but their mortality rate was the lowest among the 5 racial/ethnic groups. We found that breast tumors in Japanese Americans were more likely to be ER+/PR+. The high overall incidence rate of breast cancer in Japanese-American women was probably driven by their extensive use of postmenopausal hormone therapy, given their relatively low body weight (18, 21). The distribution of ER/PR subtypes in Native Hawaiians resembled that in the Japanese (i.e., their tumors were more likely to be ER+/PR+). The Hawaiians' high breast cancer mortality rate was probably driven by their delayed access to health care, as has been previously shown (22).

Consistent with data from other cohort studies (10, 11, 23) and with conclusions drawn from qualitative (7) and quantitative (8) reviews of epidemiologic studies, we found that age at menarche, age at first birth, and use of hormone therapy were mainly associated with ER+/PR+ tumors and not with ER−/PR− tumors. These data provide additional support for the hypothesis that these risk factors exert their effect on breast cancer through hormonal mechanisms.

Obesity is one of the established risk factors for postmenopausal breast cancer. Consistent with results from other prospective cohort studies (10, 11, 13, 24), we found that obesity increases the risk of ER+/PR+ tumors but not ER−/PR− tumors. The increased risk associated with obesity can be explained by the fact that adipose tissue is the primary source of estrogens after menopause and that obesity is associated with lower levels of sex hormone-binding globulin, a protein that binds and restricts the biologic activity of estrogens.

Two other established breast cancer risk factors, alcohol consumption and a family history of breast cancer, were associated with increased breast cancer risk for all ER/PR subtypes. The major underlying mechanism for the positive association between alcohol intake and breast cancer remains elusive. In experimental studies, alcohol consumption has been shown to affect circulating levels of estrogens (25, 26). Interestingly, in our study, the association was stronger in ER−/PR− tumors than in ER+/PR− tumors, suggesting that, in addition to a hormone-dependent mechanism, alcohol's action in breast carcinogenesis could also be mediated by hormone-independent mechanisms, such as induction of carcinogenesis and DNA damage by the alcohol metabolite acetaldehyde and by reactive oxygen species (27). Our findings are consistent with results from some cohort studies (10–12) but not all (14, 15). The finding for family history is consistent with results from most studies (7, 11) and suggests that genes involved in breast cancer heritability may not necessarily be hormone-related.

Our study had several strengths and limitations. The strengths included its large size and prospective design, the completeness of follow-up through SEER registries, and the ability to include many established breast cancer risk factors and adjust for multiple potential confounders. One limitation is that we used ER/PR data from SEER registries which were derived from medical reports generated by numerous pathologists and laboratories. Although it is possible that assay methods and cutoffs varied between laboratories, it is unlikely that they varied systematically with breast cancer risk factors or accounted for any observed differences in risk factor profiles across ER/PR subtypes. Another limitation was the absence of ER/PR data in 22% of cases and their exclusion from our analysis. Our results may have been biased if the excluded cases differed from cases that remained in the analysis with regard to risk factors and unknown confounders. However, we found that these cases were similar to the included cases with respect to breast cancer risk factors; thus, we do not consider this exclusion to have been a major source of bias. Finally, we based our analysis on data collected at baseline, and thus we did not consider changes taking place during follow-up.

In conclusion, these results provide additional prospective data showing differences in ER/PR distribution in breast tumors across racial/ethnic groups and differences in risk factor profiles for different ER/PR subtypes. The accumulating epidemiologic and genetic data indicate etiologic heterogeneity of hormone receptor-defined subtypes. Future studies of hormone receptor-negative breast cancer should focus on African-American and Latina women, as they are more susceptible to this clinically aggressive subtype.

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Appendix Table. Distribution of Risk Factors Among Breast Cancer Cases, by Availability of Information on Hormone Receptor Status[a], Multiethnic Cohort Study, 1993–1996 to 2004/2005

Characteristic	Known ER/PR Status (n = 2,543)	Unknown ER/PR Status (n = 727)
Body mass index[b], %		
<25	46.1	44.4
25–<30	32.2	31.3
≥30	21.7	24.3
Age (years) at menarche, %		
≤12	51.2	53.4
13–14	38.4	35.5
≥15	10.4	11.0
Age (years) at first livebirth, %		
Nulliparous	16.1	14.6
≤20	22.8	23.7
21–30	53.3	52.5
≥31	7.9	9.2
Parity, %		
Nulliparous	16.1	14.6
1	12.1	12.2
2–3	46.8	45.8
≥4	25.0	27.4
Type of menopause, %		
None (premenopausal)	13.5	10.7
Natural menopause	55.8	60.9
Oophorectomy	13.4	13.6
Hysterectomy	17.3	14.8
Postmenopausal hormone therapy, %		
Never use	44.8	47.9
Former use	16.7	13.8
Current use of estrogen therapy	14.5	13.4
Current use of estrogen-progestin therapy	24.1	25.0
Alcohol intake (drinks/day), %		
0	58.4	61.5
<2	34.1	31.9
≥2	7.4	6.6
Family history of breast cancer, %		
No	82.0	84.9
Yes	18.0	15.1

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.
[a] Standardized to the race/ethnicity distribution of breast cancer cases in the study.
[b] Weight (kg)/height $(m)^2$.