Breast Cancer in a Multiethnic Cohort in Hawaii and Los Angeles: Risk Factor-adjusted Incidence in Japanese Equals and in Hawaiians Exceeds that in Whites[1]

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Abstract

Few data exist on the extent to which the differences in breast cancer risk between "racial-ethnic" groups in the United States (US) are "explained" by differences in their distribution of risk factors. We have determined this for African-American (AA), native Hawaiian (NH), Japanese-American (JA), Latina-US-born (L-US), Latina-non-US-born (L-NUS), and white (W) women using prospective incidence data on 88,712 postmenopausal women recruited in 1993–1996. We identified 1,757 incident breast cancer cases through 1999 among these women (1,116 cases after excluding women with a simple hysterectomy or missing risk factor data). Data were available on seven "known" risk factors: ages at menarche and first birth; parity; age at and type of menopause; weight; hormone replacement therapy use; and alcohol consumption. The relative risks (RRs) of breast cancer (with the RR in Ws set to 1.0) for the groups were as follows: W = 1.0; AA = 0.78; NH = 1.33; JA = 0.99; L-US = 0.77; and L-NUS = 0.60. After adjustment for the risk factors, the RRs were as follows: W = 1.0; AA = 0.98; NH = 1.65; JA = 1.11; L-US = 0.95; and L-NUSB = 0.84. The slightly greater risk of the JAs compared with the Ws is in sharp contrast to the very low breast cancer rates that were observed in "traditional" Japanese women and in early Japanese migrants. The adjusted RR of NHs is 65% greater than that of Ws, and that of migrant Latinas is 16% lower than that of Ws. Elucidating the causes of the high rates in NHs is now a major focus of our efforts.

Introduction

To investigate the relationship of dietary and genetic factors to cancer risk, we established a large population-based multiethnic cohort of adult men and women aged 45–75 years in Hawaii and California over the period 1993–1996 (1). Initially, four ethnic groups (AAs,[3] JAs, Latinos, and non-Latino Ws) were selected for the study based on the size of populations in the two areas and on the striking differences between them in the reported incidence rates for several common cancers. Subsequently, NHs were added to the study. Ethnic minorities have not been well represented in epidemiological research on cancer in the US, and we believe that the differing dietary patterns and genetic make-up of the different groups will lead to insights into the etiology of cancer possibly not discernible in studies of single groups.

In this report, we compare breast cancer incidence in the different ethnic groups and the relationship of the incidence rates to the established breast cancer risk factors. Such an analysis provides essential background information to the study of how diet and genetics may affect breast cancer risk and should show where we need to concentrate our efforts to further our understanding of the etiology of this disease.

Materials and Methods

Study Population

Because drivers' license files in both Hawaii and California include the names of most resident adults, encompass all socioeconomic strata, and contain information on age and sex, we selected this source as the primary sampling frame for the study. Our focus was on NHs, JAs, and Ws in Hawaii and on AAs and Latinos in California. An additional source of subjects in Hawaii was the voters' registration file, which was used to identify names not on the drivers' license file, especially among older JA women. In California, by a combination of selective sampling by surname and choice of census tracts with a majority of AAs and use of the Health Care Financing Adminis-

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[3] The abbreviations used are: AA, African-American; JA, Japanese-American; L-NUS, Latina-non-United States-born; L-US, Latina-United States-born; NH, native Hawaiian; W, white; ERT, estrogen replacement therapy without an added progestin; EPRT, estrogen-progestin replacement therapy; HRT, hormone replacement therapy; US, United States; RR, relative risk; BMI, body mass index.

tration files, we were able to access the appropriate ethnic populations to recruit to the study. Subjects were recruited to the study by mail and entered the cohort by completing a self-administered questionnaire. Recruitment to the cohort began in 1993 and was completed in 1996. Estimated response rates among women were as follows: AAs, 25.5%; JAs, 51.3%; NHs, 42.4%; Latinas, 21.3%; and Ws, 47.0%. The cohort members completed a 26-page questionnaire that included information on height and weight, menstrual and reproductive history, the use of oral contraceptives and menopausal HRT, and a few questions on physical activity. Additional details concerning the cohort can be found in the article by Kolonel *et al.* (1, 2).

In this report we have classified the female cohort members into six "racial-ethnic" groups based on self-report: AAs; NHs; JAs; L-US; immigrant Latinas born in Mexico or South or Central America (L-NUS); and Ws. Immigrant Latinas do not include migrants from Cuba because they are in many ways not comparable with the overwhelming majority of other Latina immigrants who were born in Mexico and Central America. The cohort also includes relatively small numbers of Chinese, Filipinas, and other ethnic groups; they are not included in this report. Persons of mixed ancestry were assigned to one of the above categories according to the following priority ranking: AA; NH; Latino; JA; and W.

Surveillance

Incident cases of cancer were identified by linkage of the cohort to the state-wide population-based cancer registries in Hawaii and California. Mortality from cancer and other causes was determined from linkages to the state death certificate files in Hawaii and California.

For the breast cancer incidence data reported here we completed linkage to the Hawaii Surveillance, Epidemiology, and End Results cancer registry to December 31, 1999; to the Los Angeles County Surveillance, Epidemiology, and End Results registry to December 31, 1999; and to the California State registry to December 31, 1998. Registration of cancers at these tumor registries is considered complete to the above dates. We completed linkage to the Hawaii and California death files to December 31, 1999.

For each woman in the analysis, follow-up time begins on the date she completes the questionnaire. Women who self-reported (on the questionnaire) a cancer of the breast, endometrium, or ovary or were recorded in any of the three tumor registries as having been diagnosed with any of these cancers before the date of the questionnaire were considered ineligible for this analysis. Members of the cohort in California who were not residents of Los Angeles County when they were enrolled in the study are considered as having follow-up to December 31, 1998. Other members of the cohort are considered as having follow-up to December 31, 1999. Individuals are censored at the date of follow-up (as defined above) except (*a*) if a breast cancer diagnosis is recorded before this date when the incident breast cancer is recorded as of this date and follow-up ceases, (*b*) if a cancer of the endometrium or ovary is diagnosed before a breast cancer diagnosis and before date of follow-up (as defined above) when censoring occurs as of the date of such diagnosis, or (*c*) date of death if before date of follow-up (as defined above). Cancers of the endometrium and ovary were considered a censoring event because treatment for these cancers is likely to involve oophorectomy, which significantly alters subsequent breast cancer incidence.

Statistical Methods

RR Modeling. Analysis of breast cancer incidence is based on log linear RR regression of subject-specific characteristics. In all analyses the variables include age (in 5-year age groups varying with follow-up) and ethnicity (six groups). Analyses presented here also cover seven known risk factors: (*a*) age at menarche; (*b*) age at first birth; (*c*) number of children; (*d*) age and type of menopause; (*e*) weight at date of questionnaire; (*f*) HRT use; and (*g*) alcohol consumption. These risk factors are referred to throughout the text as the "seven known risk factors."

In the RR regression model, an individual's age group-specific hazard, $\lambda_i(t)$, of breast cancer at age group t is modeled as $\lambda_i(t) = \lambda_0(t)f(x,\beta)$, where the RR function, $f(x,\beta)$, is log linear in form, *i.e.*, $f(x,\beta) = exp(x'\beta)$, and relates "exposures" of interest, x, to breast cancer risk relative to the age group-specific baseline rates $\lambda_0(t)$. The parameter vector β is estimated by the analyses. The multivariate x can include categorical and continuous variables. Ethnic group is treated as a categorical x with the reference category being Ws.

In the tables, the RRs (other than for ethnicity) associated with x are assumed to be the same across all six ethnic groups. We tested for differences in these RRs by the log-likelihood approach (*i.e.*, fitting separate parameters for each ethnic group and testing for improvement in the model fit); we found no statistical evidence of differences. We also tested for statistically significant interactions between the risk factors, and no statistically significant improvements in the fit of the model were found.

A computationally and statistically efficient method for fitting models of this form to data from cohort studies is to create summary tables of cases and person-years of observation grouped by categories defined by age, ethnicity, and x. We use the DATAB program (Hirosoft Software, Hirosoft International Corp., Seattle, WA) to form the person-year and number of cases tables of interest for x defined as categorical variables. $\lambda_0(t)$ corresponds to a piecewise constant hazard model; Poisson regression methods are applied to estimate β (3). The number of cases in any specific cell of the table (defined by t and x) is treated as a Poisson random variable with mean equal to the value of $\lambda_0(t)f(x,\beta)$ for that cell, multiplied by the number of person-years of observation falling in that cell, with the RR parameters, β, and background rates $\lambda_0(t)$ estimated in the course of the fitting. We use the AMFIT program (Hirosoft Software) to fit the Poisson regression model. Fitting of continuous exposure effects, *i.e.*, allowing $f(x,\beta)$ to be exponential in continuous x, is accomplished by forming a categorized version of x using cut points, and the categorized x is then included in the table definitions. AMFIT then calculates the mean of the continuous version of x for each cell of the table, and these means are used as the exposure variable in the Poisson regression. This approach is also used to construct tests for trend of risk in x. Compared with Cox regression, the Poisson regression approach to fitting RR models gives very similar estimates of β and associated variances and covariances (with the degree of similarity increasing with the number of cut points used for age and x) at considerable computational savings for large cohorts (3).

Age at and Type of Menopause. Age at natural menopause (as a surrogate for the ceasing of ovarian "function") is an important breast cancer risk factor that needs to be adjusted for in comparative analyses such as we have undertaken here. It is also an important confounder in evaluating and adjusting for the effects of HRT use. We have demonstrated that alternative methods for assigning an age at menopause to women undergoing a hysterectomy without oophorectomy (simple hysterectomy) before menopause will lead to substantially biased estimates of HRT effects on breast cancer risk (4, 5), and we have

Table 1 Incident breast cancer cases among postmenopausal women

	W	AA	NH	JA	L-US	L-NUS	Total
All postmenopausal women							
No. of women	20,794	18,527	5,918	23,638	9,874	9,961	88,712
No. of breast cancer cases	462	348	157	514	168	108	1,757
RRs	1.0	0.80	1.31	0.95	0.74	0.51	
Incidence rates[a]	339.5	269.9	444.8	321.6	250.2	172.8	
All women with natural menopause or bilateral oophorectomy							
No. of women	14,079	9,527	3,636	16,576	5,930	5,616	55,364
No. of breast cancer cases	306	175	95	366	103	71	1,116
RRs	1.0	0.78	1.33	0.99	0.77	0.60	
Incidence rates[a]	319.1	250.2	424.4	314.3	245.4	192.7	

[a] Adjusted to 1970 US Standard Population ages 45–79 years. This is calculated for Ws, and the incidence rates for other groups are computed by multiplying this figure by the RRs.

argued that such women should be eliminated from consideration in studies of the effects of HRT and similarly in comparative studies such as we have undertaken here. They have been excluded in this analysis of the extent to which certain known risk factors "explain" the differences in the breast cancer rates in the different ethnic groups.

Age at last menstrual period cannot be used to uniformly estimate age at menopause because women who use sequential EPRT often continue to have monthly menstrual periods, irrespective of their ovarian function, and women on estrogen replacement therapy and continuous combined replacement therapy can rarely distinguish breakthrough bleeding from ovarian function-determined menses. For a woman taking HRT before her reported age at last menstrual period, we set her age of menopause as the year in which she began HRT use (excluding use of progestin alone), with the rationale that HRT use was started because of menopausal symptoms. This is the same schema to approximate age at menopause as we used in earlier studies of HRT and endometrial and breast cancer (6, 7).

Results

In this report we have only considered "postmenopausal" women, *i.e.*, women who reported having stopped their natural periods (see "Age at and Type of Menopause").

Table 1 shows that 88,712 eligible postmenopausal women in the 6 "ethnic" groups were recruited to the cohort. As of the cutoff date for this analysis, we had recorded 1,757 incident breast cancer cases among these women. The RRs of breast cancer (relative to the risk in Ws) are shown in the table, as well as the incidence rates adjusted to the 1970 US Standard Population ages 45–79 years.

NHs had by far the highest incidence of breast cancer, with an estimated 31% higher rate than that of the Ws (RR = 1.31, estimated as described in "RR Modeling"). The rate of breast cancer in the JAs was only 5% lower than that of the Ws. The other three ethnic groups had lower rates than the Ws: rates were 20% lower in the AAs; 26% lower in the L-US; and 49% lower in the L-NUS.

The major known breast cancer risk factors that we have comparative data on are age at and type of menopause, age at menarche, age at first birth, number of children, weight, HRT use, and alcohol consumption.

Type of menopause varies considerably between the groups (Table 2). The AA women have a greater frequency of simple hysterectomy (27.5%) than do the Ws (18.7%), whereas the JAs have a much lower frequency of simple hysterectomy (12.9%). After excluding the women with a simple hysterectomy for the reasons discussed in "Materials and Methods" and women with any missing information on the other known risk factors, the total number of women in the 6 ethnic groups was reduced to 55,364 with 1,116 incident breast cancer cases (bottom half of Table 1). The comparisons between ethnic groups are modified only slightly by these restrictions.

After excluding women with a simple hysterectomy, the AAs have the highest proportion of bilateral oophorectomies (29.1%), the L-NUS have the lowest proportion of bilateral oophorectomies (12.9%), with the proportions in the other groups being around 21%, as shown in Table 2. Among women with bilateral oophorectomies, the AA women had the operation performed earlier. The main effect of these differences in bilateral oophorectomy frequency and age would be to reduce the breast cancer rate of the AA women.

The only major difference in age at menarche is a late age in the L-NUS (Table 3); this would decrease their breast cancer rate.

There are major differences between the different ethnic groups in age at first birth and number of children. The AAs and NHs have an earlier first birth with 45.3% and 43.3% of them, respectively, having a first birth before age 20 years. These figures are a little lower in the Latinas (~39%), whereas 23.4% of the Ws and only 9.1% of the JAs have such an early first birth. The L-NUS and Hawaiians have more children (55.5% and 54.8%, respectively, had four or more children), whereas the JAs have the fewest (19.0% had four or more children). The major effects of these differences would be to reduce the breast cancer rate in the AAs, Hawaiians, and Latinas and to increase the rate in the JAs.

Table 4 shows that the AAs are the heaviest as a group, and, despite their greater average height (data not shown), they have the greatest BMI (mean BMI of 28.9 kg/m^2; data not shown). The mean BMI of the Hawaiians is lower at 28.0 kg/m^2, equal to that of the L-US. The mean BMI of the L-NUS is a little lower at 27.4 kg/m^2. The Ws in the cohort have a much lower mean BMI of 25.6 kg/m^2. The JAs weighed much less than any other group, and, despite the fact that they are shorter on average than any other group, their mean BMI is only 23.5 kg/m^2. The major effects of these differences would be to reduce the JA breast cancer rate and to increase the breast cancer rate in the AAs and to a lesser extent in the other groups compared with the Ws. (Note: the fitted model included weight but not height or BMI; after fitting weight, neither height nor BMI was statistically significant, and weight alone provided the best fit of these variables considered separately.)

Current HRT use is a significant risk factor in the cohort (Table 4). The JAs and Ws used HRT to a much greater extent than the other groups (~31% were current users of EPRT). Approximately 18% of Hawaiians and L-US were current users

Table 2 Distribution of type of menopause with associated RRs of breast cancer

	W	AA	NH	JA	L-US	L-NUS	RR[a]	*P*[a]
All women[b]								
Natural	62.7%	51.4%	63.8%	69.2%	60.5%	72.6%		
Bilateral oophorectomy	18.6%	21.1%	18.3%	17.8%	16.1%	10.8%		
Simple hysterectomy	18.7%	27.5%	17.8%	12.9%	23.5%	16.6%		
Excluding women with simple hysterectomy[c]								
Natural	77.3%	70.8%	77.8%	79.5%	79.1%	87.1%		
Bilateral oophorectomy	22.7%	29.1%	22.2%	20.5%	20.9%	12.9%		
Age at natural menopause (yrs)								
≤44	11.7%	14.7%	15.0%	9.0%	16.8%	20.6%	1.00	
45–49	24.8%	22.3%	23.0%	22.3%	25.4%	30.1%	1.04	
50–54	32.5%	26.0%	30.0%	38.4%	30.1%	29.2%	1.21	
55+	8.2%	7.9%	9.8%	9.8%	6.7%	7.2%	1.31	
Age at bilateral oophorectomy (yrs)								
≤44	13.1%	19.0%	12.8%	10.0%	12.6%	7.6%	0.84	
45–49	6.4%	7.2%	6.2%	7.2%	5.6%	3.6%	0.97	
50+	3.2%	3.0%	3.2%	3.4%	2.8%	1.7%	1.04	0.002[d]

[a] *P* = two-sided significance test; RR, RRs fitting all seven known risk factors and ethnicity to data on women with natural menopause or bilateral oophorectomy.
[b] Standardized to the age distribution of the cohort as in Table 1.
[c] Standardized to the age distribution of the remaining cohort.
[d] Test for type of menopause and separate linear trends for age at natural menopause and age at bilateral oophorectomy (3 degrees of freedom) after fitting all seven known risk factors and ethnicity.

Table 3 Distributions of age at menarche, age at first birth, and number of children with associated RRs of breast cancer among women with natural menopause or bilateral oophorectomy

	W	AA	NH	JA	L-US	L-NUS	RR	*P*
Age at menarche[a] (yrs)								
≤12	48.3%	49.1%	55.1%	48.2%	56.5%	35.7%	1.00	
13–14	40.7%	38.1%	34.1%	38.8%	34.3%	44.6%	0.88	
15+	11.0%	12.8%	10.8%	12.9%	9.2%	19.8%	0.81	0.01[b]
Age at first birth[a] (yrs)								
Never	16.3%	12.5%	7.0%	13.8%	9.0%	9.2%	1.00	
≤20	23.4%	45.3%	43.3%	9.1%	39.4%	37.8%	0.74	
21–30	53.5%	37.3%	47.1%	67.7%	47.9%	44.9%	0.89	
31+	6.8%	5.0%	2.6%	9.3%	3.6%	8.1%	1.07	<0.001[c]
Children of parous women[a,d]								
1	11.7%	15.8%	5.9%	11.3%	6.9%	7.3%	1.00	
2–3	47.7%	36.1%	32.3%	55.9%	37.1%	28.1%	0.96	
4+	24.2%	35.7%	54.8%	19.0%	46.9%	55.4%	0.83	0.05[b]

[a] Standardized to the age distribution of the cohort of women with natural menopause or bilateral oophorectomy.
[b] Test for trend (for this variable) after fitting all seven known risk factors and ethnicity.
[c] Heterogeneity test (for this variable) after fitting all seven known risk factors and ethnicity.
[d] This is to test for effect of increasing parity after adjusting for age at first birth (and nulliparity).

of EPRT, and use was much less frequent in the L-NUS and AAs (~10% were current users of EPRT). The effects of these differences would be to decrease breast cancer rates in the Hawaiians and L-US relative to the Ws and to decrease rates to a greater extent in the L-NUS and AAs.

Current alcohol consumption was significantly associated with risk of breast cancer in the cohort. Women consuming 1 or more drinks/day had a 39% increase in risk compared with nondrinkers. The Ws consumed alcohol to a much greater extent than the other groups, with 22.5% consuming 1 or more drinks/day. The comparable figure for AAs and NHs was ~9%; this decreased to 6% for L-US and to ~3.5% for L-NUS and JAs. The effects of these differences would be to decrease breast cancer rates in all other groups compared with the Ws, with the largest effects in the L-NUS and JAs.

Table 5 shows our estimates of how these ethnic differences in the distributions of these risk factors would affect breast cancer rates under the assumption that the RRs associated with the risk factors are as found in this study (vertical columns marked RR in Tables 2 - 4). When the seven known risk factors are taken into account, the RR of the AAs should be 20% lower than that of the Ws, the RR of the NHs should be 19% lower than that of the Ws, the RR of JAs should be 10% lower than that of the Ws, the RR of L-US should be 18% lower than that of the Ws, and the RR of the L-NUS should be 28% lower than that of the Ws. These expected RRs (expected on the basis of the different distributions of the risk factors) are compared with the observed (estimated) RRs of breast cancer in the next line of the table.

The observed RR of breast cancer of AAs (0.78; compared with the Ws) is close to that predicted solely on the basis of their distribution of risk factors (0.80). This is confirmed by the observed RR adjusted for the risk factors being close to 1.

The observed RR of breast cancer of the NHs (1.33) is not at all predicted on the basis of their distribution of risk factors, which predict that they should have a 19% reduced RR, rather than a 35% increased RR. Their observed RR adjusted for the risk factors is 1.65.

The observed RR of JAs is equal to that of the Ws,

Table 4 Distributions of weight, HRT, and alcohol consumption with associated RRs of breast cancer among women with natural menopause or bilateral oophorectomy

	W	AA	NH	JA	L-US	L-NUS	RR	*P*
Weight (kg)[a]								
<57.0	21.9%	7.7%	15.4%	57.9%	15.6%	16.6%	1.00	
57.1−	30.8%	18.6%	24.4%	27.1%	27.4%	32.2%	1.11	
66.1−	26.9%	31.2%	28.1%	11.6%	30.5%	32.4%	1.21	
77.0+	20.3%	42.5%	32.1%	3.5%	26.5%	18.8%	1.34	
Average	68.2	77.5	73.2	56.7	71.0	68.3		0.003[b]
HRT								
Never	35.7%	55.1%	52.2%	39.8%	49.3%	62.6%	1.00	
Past HRT	19.4%	23.1%	18.5%	14.3%	20.2%	19.6%	1.05	
Current ERT	14.3%	11.3%	10.9%	15.2%	12.8%	7.4%	1.36	
Current EPRT	30.6%	10.5%	18.3%	30.7%	17.7%	10.3%	1.86	<0.0001[c]
Alcohol (drinks/day)								
Never	40.1%	62.0%	63.8%	77.7%	60.3%	68.9%	1.00	
<1	37.4%	28.5%	26.8%	18.9%	33.6%	27.5%	1.08	
≥1	22.5%	9.5%	9.3%	3.4%	6.1%	3.6%	1.39	0.002[b]

[a] Standardized to the age distribution of the cohort of women with natural menopause or bilateral oophorectomy.
[b] Test for linear trend (for this variable) after fitting all seven known risk factors and ethnicity.
[c] Test for heterogeneity after fitting all seven known risk factors and ethnicity.

Table 5 Predicted and observed RRs of breast cancer among women with natural menopause or bilateral oophorectomy

Risk factor	RRs					
	W	AA	NH	JA	L-US	L-NUS
Predicted						
Menopause	1.00	0.98	1.00	1.02	0.99	1.00
Menarche	1.00	1.00	1.01	1.00	1.01	0.98
Age at first birth	1.00	0.96	0.95	1.03	0.96	0.97
No. of children	1.00	0.99	0.95	1.01	0.96	0.95
Weight	1.00	1.06	1.03	0.92	1.02	1.01
HRT	1.00	0.86	0.91	1.00	0.91	0.85
Alcohol	1.00	0.95	0.95	0.92	0.94	0.93
Combined	1.00	0.80	0.81	0.89	0.81	0.72
Observed						
Adjusted for age	1.00	0.78	1.33	0.99	0.77	0.60
Adjusted for age and all 7 known risk factors (with 95% confidence interval)	1.00	0.98 (0.80–1.19)	1.65 (1.30–2.09)	1.11 (0.93–1.33)	0.95 (0.75–1.20)	0.84 (0.64–1.10)

whereas their rate should be 11% lower on the basis of their distributions of risk factors (mainly weight and alcohol differences). Their observed RR adjusted for the risk factors is 1.11.

The observed RR among the L-US is 0.77, slightly lower than the predicted RR of 0.81. Their observed RR adjusted for the risk factors is 0.95.

The observed RR among the L-NUS is 0.60, 16% lower than their predicted RR of 0.72. Their observed RR adjusted for the risk factors is 0.84.

Discussion

Our results show clearly that the risk of breast cancer in the NH women far exceeds that in the Ws and that the risk factor-adjusted risk of breast cancer in the historically very low-risk JAs also appears to exceed the risk in Ws. Only the risk in the immigrant Latinas is lower than that of the Ws.

The slight excess in breast cancer risk of the JAs compared with the Ws is most striking. This comparison is in sharp contrast to the very low breast cancer rates that were observed in "traditional" Japanese women and in early Japanese migrants, which were only one-sixth the rates of US women (8). The breast cancer rates in Japanese migrants to Hawaii and California were noted to be increasing as early as 1960 (9). The transition to at least US rates is now clearly complete (at least with regard to postmenopausal women). We previously showed that the 6-fold difference between the US rates and the rates in traditional Japanese could be explained by a combination of their late age at menarche, their very low weight, low premenopausal ovarian estrogen and progesterone serum levels, and low postmenopausal estrogen levels (10–12). The JA women in the cohort have a risk factor distribution that predicts that their breast cancer rate should be lower than that of the Ws, mainly due to lower weight and a much lower level of alcohol consumption. We will need further follow-up of the cohort to confirm their adjusted increased risk compared with the Ws.

Another most interesting finding is the very high breast cancer rates of NHs. The distribution of their breast cancer risk factors predicts that their breast cancer rates should be much lower than that of Ws. However, their observed relative rate of breast cancer is 33% greater than that of the Ws, and after adjustment for their distribution of risk factors, their underlying breast cancer rate is 65% greater than that of Ws. We would speculate that their endogenous premenopausal serum estrogen and/or progesterone levels are greater than that of the Ws and that their elevated breast cancer risk in the postmenopausal period is a carryover effect of

this. Elevated postmenopausal serum estrogen levels could also contribute to the increased rate; preliminary data we have collected suggest that their postmenopausal serum estradiol levels may be as much as 20% higher than that of any other group. If correct, an explanation could relate to differences in their distribution of genetic polymorphisms in the sex steroid and gonadotropin metabolism pathways. We have found evidence that polymorphisms in at least two genes in the sex steroid pathway, *CYP17* and *HSD17B1*, may affect serum estrogen levels (13, 14). We have collected data on the distribution of the number of "high-risk" alleles for *CYP17* and *HSD17B1* in women from the different racial-ethnic groups; 42% (119 of 283) of the NHs have 3 or 4 high-risk alleles, whereas only ~25% of women in each of the other groups have 3 or 4 high-risk alleles. This difference could be a significant contributor to the increased breast cancer risk of NHs. Another possibility is that their insulin-like growth factor levels may be elevated. Finally, dietary factors may play a significant role.

The observed breast cancer risk of the AAs in the cohort is some 22% lower than that of the Ws. This can be almost completely explained by their distribution of risk factors. AAs have been observed to have greater premenopausal rates of breast cancer than that of Ws, a phenomenon that has been seen in cancer registry data for decades (15). The reason for this is likely to be elevated premenopausal serum estrogen and progesterone levels (16–18).[4] We have found that their endogenous postmenopausal serum estrogen (estradiol and estrone) levels are certainly no lower than that of Ws, even after adjusting for weight (19). If the AA population that comprises our cohort had elevated premenopausal breast cancer rates, as we would suspect, then the question is why this elevation does not persist into the postmenopausal period.

The observed breast cancer risk of L-US is 23% lower than that of the Ws. Almost all of this difference is explained by their younger age at first birth, greater number of children, low frequency of use of HRT, and low alcohol use. After adjusting for the risk factors, their RR of breast cancer is only 5% lower than that of the Ws.

The breast cancer risk in the migrant Latinas is 40% lower than that of the Ws. A significant proportion of their lower risk is explained by their later age at menarche, younger age at first birth, greater number of children, low frequency of use of HRT, and very low alcohol use, so that their adjusted breast cancer risk is only some 16% lower than that of Ws. The reasons for this are not clear, but this lower risk may be due to dietary habits that remain distinct from that of Ws (1).

Our questionnaire included a few questions on current physical activity. Inclusion of these questions did not lead to any improvement in the fit of the risk factor model. Differences in physical activity as teenagers and as young adults may well affect breast cancer risk (20) and may be part of the explanation of the increased risk of NHs, but the magnitude of this effect is unlikely to explain more than a small amount of their greatly increased risk.

We did not collect any information on breast feeding. Differences in breast feeding may be part of the explanation for the low breast cancer rates in migrant Latinas, and we will be collecting information on this factor.

[4] C. A. Haiman, M. C. Pike, L. Bernstein, V. Jaque, F. Stanczyk, A. Afghani, R. K. Peters, P. Wan, and L. Shames. Ethnic differences in ovulatory function in nulliparous women, submitted for publication.

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