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13. ABSTRACT *(Maximum 200 Words)*

With funding from the Department of Defense, the National Cancer Institute, and the California Breast Cancer Research Program we conducted a population-based case-control study of breast cancer in women aged 35-79 who self-identified as Latina, African-American or White. Based on interview data on 1290 cases and 1611 controls, we found that lifetime physical activity reduced breast cancer risk in all three racial/ethnic groups. Phytoestrogen intake was not associated with risk. The data suggest that vitamin D exposures may reduce risk among Whites. Associations with these newly hypothesized factors and with the standard breast cancer risk factors (i.e., demographic and personal characteristics, menstrual and reproductive factors, body size characteristics) were generally similar across the three racial/ethnic groups, but there was considerable variation in exposure prevalence rates. For some, but not all of the exposures considered, the prevalence rates paralleled the incidence rates in the three populations. We estimated relative attributable risk fractions and found that the factors evaluated in this study explained a larger proportion of the differences in incidence among younger women (aged 35-49) than older women (aged 50-79). Also, the factors considered explained more of the difference in incidence between Latinas and Whites than between African-Americans and Whites.

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1. INTRODUCTION

1.1. Racial/ethnic differences in breast cancer incidence

One of the most striking features of breast cancer is the ten-fold variation in incidence across populations from different countries [Parkin 1997]. Among the cancer registries contributing incidence data to the "Cancer In Five Continents" series, the incidence rates (per 100,000, age-standardized to the 1970 world population) in 1988-92 were highest in non-Hispanic White women living in Los Angeles (103.7) and San Francisco (103.3), and lowest (less than 10) among Asian women living in India, Korea, and Thailand. Considerable variations in incidence rates are also observed among various Latin American groups. In 1988-92, incidence rates ranged from 27 to 93 [Parkin 1997]. They were lowest in Ecuador, Peru, Costa Rica, and Columbia ranging from 27-32; intermediate in Puerto Rico (46); and highest in Argentina (60) and Uruguay (93). In Brazil, they ranged from 30-62.

Breast cancer incidence rates vary considerably between racial/ethnic groups in the US. In 1994-1998, the average incidence rate (per 100,000) in the San Francisco Bay area was highest in White women (132), followed by African-Americans (94), Latinas (78), and Asians (73) [Li 2001]. Despite the lower incidence in African-Americans, Latinas, and Asians, breast cancer is the leading cancer in these populations, accounting for 29-30% of all cancers diagnosed, a proportion that is similar to that in Whites (33%).

Incidence rates also vary among Latinas residing in the US. In 1988-92, lower rates were reported for Hispanics living in Central California (54), Los Angeles (57), and New Mexico (61) than in San Francisco (71) [Parkin 1997]. This variation in incidence among Latinas is likely due to differences in country of birth, duration of residence in the US, educational background and related reproductive and lifestyle factors (see section 2.2.4).

Age-specific incidence rates generated from publicly available data from the SEER cancer registry show that among women under age 40, incidence rates in 1992-1997 were highest among African-American women, followed by Whites, Asians, and Hispanics (Figure 1, and for more detail Figure 2). Among women aged 40-64, age-specific incidence rates were highest among Whites, followed by African-Americans, Latinas and Asians. Among women aged 65 and older, incidence rates were highest among Whites, followed by African-Americans, Hispanics, and Asians. Thus, cross-overs in incidence curves occur at age 40 for African-Americans and Whites, and at age 65 for Hispanics and Asians.

Figure 3 presents incidence rates in the San Francisco Bay area from 1973 to 1998 for Whites, African-Americans, and Hispanics [Glaser 1995, Li 2001]. Average 5-year incidence rates for the periods 1973-77, 1978-82, 1983-87, 1988-92, and 1994-1998 are shown. Among African-Americans and Hispanics, incidence rates were highest in 1988-92 and declined thereafter. The percent increase from 1973-77 to 1988-92 was 34% among Hispanics and 25% among African-Americans. Whites experienced a similar increase during this time period (24%), though their incidence further increased in 1994-98 (3.1%). These trends are similar to national trends.

1.2. Racial/ethnic differences in breast cancer etiology

Despite efforts for many years, the major risk factors for breast cancer do not fully explain the incidence of breast cancer. Population attributable risk fractions (PAR) have been estimated for US White populations [Seidman 1982, Bruzzi 1985, Madigan 1995, Rockhill 1996, Brinton 1997, Rockhill 1998] and populations in Italy [Tavani 1997, Mezzetti 1998] and China [Gao 2000]. Though incidence rate vary greatly between the US, Italy, and China, the PAR were similar, ranging from 21-55%. It is well known, however, that PAR estimates are sensitive to changes in exposure cutpoints [Rockhill 1998]. Only two reports estimated PAR for African-American women [Rockhill 1996, Brinton 1997]. Established risk factors explained a smaller proportion of disease occurrence in African-Americans (6%) than Whites (20%) [Rockhill 1996].

Similarly, the currently established risk factors do not fully explain the striking international differences in breast cancer incidence [Hsieh 1990, Smith-Warner 1998], though changes in menstrual and reproductive patterns seem to play a major role in low risk populations that experience rapid increases in breast cancer incidence (e.g., Chinese women) [Gao 2000]. Colditz [1997] estimated that differences in reproductive patterns (i.e., 6 or more pregnancies versus 2 pregnancies) explain at least 50% of the international differences in breast cancer incidence rates.

Relatively few analytic studies of breast cancer with an etiologic focus have been conducted in multiethnic populations in the US that would help us better understand the reasons for the observed racial/ethnic differences in incidence rates. Furthermore, not all studies presented separate results for Latinas [the CASH study: Mayberry 1994a; the New Mexico Health Study: Gilliland 1998, Baumgartner 2000, Li 2001, Gilliland 2001] and African-Americans [Austin 1979; Schatzkin 1987; Hiatt 1988; Amos 1991; the CASH study: Mayberry 1992, Mayberry 1994b; Krieger 1994; Palmer 1995a; Palmer 1995b; Brinton 1995; Brinton 1997; and the Carolina Breast Cancer Study: Moorman 2000, Hall 2000, Kinney 2000, Moorman 2001, Adams-Campbell 2001] that allow for direct racial/ethnic comparisons of risk factors.

The pronounced racial/ethnic differences in breast cancer incidence between Latinas, African-Americans, and White women remain largely unexplained [Nomura 1984, Brinton 1997, Gilliland 1998, Pathak 2000, Maskarinec 2000]. It is not known to what extent the differences in incidence rates are attributable to racial/ethnic differences in (1) the magnitude of relative risks associated with known and suspected risk factors, (2) the prevalence of known and suspected risk factors, (3) the magnitude of relative risks and/or prevalence of risk factors yet to be identified, and (4) genetic susceptibility. To date, only two studies estimated relative attributable risk fractions (RAR) for African-Americans and Latinas compared to Whites [Brinton 1997, Gilliland 1998]. Gilliland [2000] estimated that in women age 50 and older, reproductive factors (i.e., parity, age at first full-term pregnancy, duration of breast-feeding) explained only 17% of the difference in breast cancer incidence between Latina and White women, and did not explain the difference in incidence in women under age 50. On the other hand, Brinton et al. [1997] concluded that among women aged 40-54 differences in prevalences and effects of menstrual and reproductive factors explained most of the difference in breast cancer incidence between White and African-American women.

1.3. Purpose of on-going research

The San Francisco Bay Area offers a unique opportunity to conduct etiologic research in a multiethnic population given the large number of breast cancer cases diagnosed each year, 25%

of whom are non-White, and the availability of a population-based cancer registry covering the San Francisco Bay Area. In 1995, Dr. Esther M. John received funding from NCI (R01 CA63446) to conduct a population-based case-control study of breast cancer risk factors in Hispanic women. Around the same time, Dr. Pamela Horn-Ross, another epidemiologist at the Northern California cancer Center received funding from the California Breast Cancer Research Program (1RB0125, PI: Pamela Horn-Ross) to conduct a case-control study of postmenopausal breast cancer in Hispanic, African-American, and White women in relation to phytoestrogen exposure. Thus, Drs. John Horn-Ross decided to administer the two studies as a single study using the same protocol and questionnaire. In 1995, Drs. John and Horn-Ross also received a NAPBC Supplement to the NCI funded study (R01 CA63446-OWH#46) to assess phytoestrogen intake in Hispanic women. A subsequent research proposal to extend this case-control study and focus on racial/ethnic differences in breast cancer risk factors was funded by the *Department of Defense in 1996 (DAMD17-96-1-6071, PI: Esther M. John).*

In the late Fall of 1999, we completed data collection for this large population-based case-control study in Hispanic, African-American, and White women, funded by NCI, BCRP, and DOD. We completed home interviews with 1,326 breast cancer patients (cases) and 1,657 women without a history of breast cancer (controls). The purpose of this case-control study was to collect interview data on a broad array of known, suspected, and newly hypothesized factors to examine racial/ethnic differences in breast cancer risk factors in a large multiracial/ethnic population from a single geographic area. This research will make a significant contribution to the lack of knowledge about the etiology of breast cancer in non-white populations and will help elucidate the reasons for the striking racial/ethnic differences in breast cancer incidence.

We report here our findings on breast cancer risk factors in 1,165 Latinas (468 cases, 697 controls), 870 African-Americans (409 cases, 461 controls), and 948 Whites (449 cases, 499 controls).

2. BODY

2.1. Technical Objective 1: ***Recruit 330 African-American and 365 White breast cancer cases and equal numbers of controls and obtain interview and anthropometric data on the established and newly hypothesized risk factors.***

Data collection for the case-control study began in May 1996 and was completed in the late fall of 1999. All work related to Tasks 1-8 in the Statement of Work have been completed. Specific accomplishments are described below for the overall study (funded by DOD, NCI, and BCRP).

2.1.1. Case ascertainment. A total of 7,591 women aged 35-79 and newly diagnosed with histologically confirmed, primary invasive breast cancer between April 1, 1995 and April 30, 1998 were identified through the population-based cancer registry covering the San Francisco Bay Area (i.e., San Francisco, San Mateo, Santa Clara, Alameda and Contra Costa counties). The cancer registry is part of the NCI SEER program and the California Cancer Registry. A total of 7,591 patients were identified through the cancer registry who were listed as Hispanic, African-American, or White in the cancer registry records. Of these, 297 (3.9%) were deceased at the time of contact.

2.1.2. Physician consent. As required by the cancer registry, each breast cancer patient's physician listed on the cancer abstract was contacted to inquire about medical or psychological contraindications prior to our contacting his or her patient. Physician-reported contra-indications were obtained for 120 (1.6%) cases.

2.1.3. Control ascertainment. Population controls were identified through random-digit dialing (RDD). We generated a total of 74,673 random numbers which were dialed up to ten times. Among the 45,378 (60.8%) telephone numbers assessed as residential, nobody was reached at 10,012 numbers despite 10 attempts (i.e., no answer or answering machine only). Among the remaining 35,366 phone numbers where a household member was reached, a household enumeration was completed for 28,775 (81.4%) telephone numbers. Among potentially eligible controls, 2,389 were randomly selected according to the race/ethnicity and 5-year age distribution of cases. Among African-Americans and Whites, controls were matched to cases in an approximate ratio of 1 control per case; among Hispanics, the ratio was 1.5 controls per case.

2.1.4. Screening interview. Trained professional interviewers tried to contact the 7,174 alive cases with physician consent by telephone and administered a brief screening questionnaire to determine study eligibility and assess self-identified race/ethnicity. Given the known misclassification of race/ethnicity, particularly among Latinas, in the cancer registry records [Swallen 1997], we contacted by telephone all Latina, African-American, and White breast cancer patients to assess self-identified race/ethnicity. In addition, the screening questionnaire inquired about current age, adoption status, Jewish heritage, personal history of breast or ovarian cancer, and history of cancer in first-degree relatives. Controls were administered the same screening interview by telephone.

Cases: A total of 6,157 (85.8%) cases completed the screening interview. Among the remaining cases, 487 (6.8%) were too ill or refused participation, 54 (0.8%) did not speak English or Spanish, 359 (5.0%) had moved or could not be located, 100 (1.4%) could not be reached despite more than 10 attempts, and 17 were not screened due to end of study.

Controls: Of the 2,389 controls selected into the study, 13 were deceased by the time they were contacted to participate in the study. Among the remaining 2,376 controls, 2,062 (86.8%) completed the brief telephone screening interview, 168 (7.1%) were too ill or refused to participate, 129 (5.4%) had moved or could not be located, 8 did not speak English or Spanish, and 9 could not be reached before the end of the study.

2.1.5. Home interview. Cases and controls meeting the eligibility criteria were invited to participate in an in-person interview which was usually conducted at the participant's home. The home visit involved the administration of the consent form, the completion of a structured questionnaire, and the measurement of anthropometry (i.e., weight, height, waist and hip circumferences), and skin pigmentation using a Minolta Chromameter. The questionnaire inquired about demographic background, physical activity, sunlight exposure, diet, supplement intake, anthropometry, residential history, occupational history, pregnancy history, menstrual history, hormone use, and medical history. Detailed descriptions of the questionnaire items are provided below in the results section under each relevant exposure variable. The questionnaire was translated into Spanish and thoroughly pre-tested both in English and Spanish. The interview and measurements took 2 to 2 1/2 hours to administer for most participants. All study participants received a compensation of $25.00 for their time and effort in completing the home interview.

Cases: Women eligible for an in-person interview included all cases who self-identified in the screening interview as Hispanic (n=535) or African-American (n=480), and a 10% random sample of cases who self-identified as White (n=524). The in-person interview was completed by 1,326 (response rate of 86.2%) cases, including 468 (87.5%) Hispanics, 409 (85.2%) African-Americans, and 449 (85.7%) Whites. Interviews were not completed due to refusal (n=149), illness (n=42), end of study (n=15), and inability to locate (n=6). One interview was excluded due to a large number of missing data items.

Controls: Controls invited to participate in the in-person interview included 806 Latinas, 563 African-Americans, and 604 Whites. Of these, 1,657 (84.0%) controls completed the home interview, including 697 (86.5%) Hispanics, 461 (81.9%) African-Americans, and 499 (82.6%) Whites. Control interviews were not completed for the following reasons: 251 refused, 30 were too ill, 15 could not be located, and 19 were not completed due to end of study. One interview was too incomplete, and thus excluded.

Summary of field work: We completed in-person interviews with 1,326 cases and 1,657 controls. Of these, 640 case and 760 control interviews were funded by the DOD. Race/ethnic-specific response rates to screening and in-person interview are presented in Table 1.

2.1.6. Quality control. Several quality control procedures were implemented to ensure the collection of high quality data. (1) All interviewers participated in a thorough training course conducted by the Principal Investigator and Program Manager to ensure data collection according to a standardized protocol. (2) Interviewers met every two weeks with the Program Manager to discuss progress and quality of the completed work. (3) Interviewers participated in quarterly staff meetings, or more often as needed, to discuss specific issues arising in the field (e.g., refusals, no-shows, home visits, organization of work load, incentives, etc), and they participated in refresher sessions on specific questionnaire items and measurements. (4) Each interviewer was observed on several occasions by the Program Manager while conducting an interview in the field. A report on the observation was prepared and discussed with the interviewer. (5) Each completed questionnaire was edited by the interviewer immediately following the interview. (6) Each edited questionnaire was reviewed by the Program Manager. Missing data items and obvious error and inconsistencies in answers were identified and clarified by re-contacting the study participant. (7) Equipment (i.e., scales, chromameters) were periodically calibrated by office staff. (8) A sample of study participants was re-contacted and questioned about specific sections of the questionnaire. (9) Double data entry was performed in order to identify data entry errors.

2.1.7. Data management. Progress in RDD and data collection (e.g., screening, in-person interview, measurements) was monitored through two computerized FOXPRO tracking systems. Data entry of screening and questionnaire data was also performed through FOXPRO data entry screens.

In preparation of the statistical analyses, the raw data were cleaned, exposure and confounder variables were defined, and analytic data files were created.

2.2. Technical Objective 2: ***Compare breast cancer risk factors among cases and controls with regard to racial/ethnic differences in the magnitude of association with the established and newly hypothesized risk factors, and prevalence of risk factors.***

We combined the interview data collected with DOD funds with those collected with funds from the National Cancer Institute (R01 CA63446) and the California Breast Cancer Research Program (1RB0125). The combined dataset includes interview data for 1,326 cases (468 Latinas, 409 African-Americans, 449 Whites) and 1,657 controls (697 Latinas, 461 African-Americans, 499 Whites). The statistical analyses addressing Technical Objective 2 are based on this combined dataset.

2.2.1. Statistical approach. We used unconditional logistic regression modeling to calculate odds ratios (OR) and 95% confidence intervals (CI) as an estimate of relative risk, while adjusting for age (five-year age groups) and other factors. For each racial/ethnic group, we assessed associations with a broad range of established and suspected risk factors for breast cancer, including: age, country of birth, education, family history of breast cancer, prior biopsy for benign breast disease, age at menarche, parity, age at first full-term pregnancy, lifetime breast-feeding, use of oral contraceptives, menopausal status, type of menopause, age at menopause, use of hormone replacement therapy (HRT), height, body mass index (BMI), waist-to-hip ratio, weight gain since age 25, lifetime physical activity, sunlight exposure and other vitamin D related factors, dietary vitamin D intake, caloric intake, fat intake, alcohol consumption, and phytoestrogen intake. In the multivariate logistic models we adjusted for all factors that were significantly associated with breast cancer risk.

We performed separate analyses by menopausal status for certain exposures (i.e., breast-feeding, body size characteristics, physical activity) that may have different effects in pre- and postmenopausal women. Women were considered postmenopausal if their periods had stopped more than 1 year prior to diagnosis/selection and they had never used HRT or used HRT only after the cessation of menses. Also included in this group were women who began using HRT prior to the cessation of menses but had attained age 55 or older at the time of diagnosis/selection, and women who reported a bilateral oophorectomy and/or a hysterectomy. Women who had begun using HRT prior to the cessation of menses but had not attained age 55 were excluded from these analyses as their menopausal/ovarian status could not be determined. The remainder of women were considered premenopausal.

Thus, we considered three sets of confounders in the logistic models:

1) Pre- and postmenopausal women combined: age (continuous), country of birth (US, non-US), education (less than 12 years, high school graduate, some college or vocational school, college graduate), family history of breast cancer in first-degree relatives (yes, no), prior biopsy for benign breast disease (yes, no), age at menarche (8-11, 12-13, ≥14), parity (0, 1-2, 3-4, ≥5), lifetime breast-feeding (0 months, <12, ≥12), lifetime physical activity (tertiles among controls), height (tertiles among controls), and interaction of menopausal status (premenopausal, postmenopausal, undetermined) and BMI (quartiles among controls).

2) Premenopausal women: variables listed above under 1), plus age at first full-term pregnancy (<20, 20-24, 25-29, ≥30), and BMI only (instead of interaction of menopausal status and BMI).

3) Postmenopausal women: variables listed above under 1), plus age at menopause (<44, 45-54, ≥55), but exclusion of BMI and prior biopsy for benign breast disease.

We performed both age-adjusted (not shown) and multivariate-adjusted (shown in Tables below) analyses. Generally, age- and multivariate-adjusted odds ratios were similar. Instances where these two sets of odds ratios differed substantially are noted in the text below.

For the calculations of relative attributable risk fractions, we also performed multivariate analyses for women under age 50 and women age 50 and older (Tables 34 and 35).

2.2.2. Analytic dataset. The study collected interview data for 1,326 cases and 1,657 controls. Of these, 82 individuals (36 cases, 46 controls) were excluded from the analytic dataset due to missing information on one or more variables we adjusted for in the multivariate analyses.

Analytic dataset; 1290 cases, 1611 controls

Analyses stratified by race/ethnicity:

Latinas:	455 cases, 677 controls
African-Americans:	397 cases, 449 controls
Whites:	438 cases, 485 controls

Analyses stratified by menopausal status:

Premenopausal:	402 cases, 482 controls
Postmenopausal:	847 cases, 1065 controls

105 women for whom menopausal status could not be determined were excluded (i.e., mostly women under age 55 who started using HRT before cessation of menstruation).

Analyses stratified by age:

Women < 50:	411 cases, 543 controls
Women ≥50:	879 cases, 1068 controls

2.2.3. Evaluation of risk factors. Based on the data collected in our questionnaire, we evaluated associations with the following risk factors:

Established or suspected risk factors	
Demographic and personal characteristics	age, country of birth, education, family history of breast cancer in first-degree relatives, prior biopsy for benign breast disease
Menstrual factors	age at menarche, menopausal status, type of menopause, age at natural menopause, age at surgical menopause
Reproductive characteristics	nulliparity, parity, age at first birth
Breast-feeding	history of breast-feeding, lifetime duration of breast-feeding, lifetime duration of breast-feeding without supplementation, average duration of breast-feeding per child, number of children breast-fed, use of medication to stop milk production
Exogenous hormone use	oral contraceptives, hormone replacement therapy
Body size characteristics	height, body mass index, waist-to-hip ratio, weight gain since age 25
Dietary factors	caloric intake, fat intake
Alcohol consumption	alcohol intake
Newly hypothesized factors	
Physical activity	exercise and sports, transportation, strenuous chores, occupational physical activity, total lifetime physical activity
Vitamin D from sunlight exposure and diet	time spent outdoors , sunlight exposure by skin pigmentation measurements, residential geographic latitude, constitutive skin pigmentation, skin reaction to sun exposure, tanning, protection from sun exposure, sunscreen use, vitamin D intake from diet and supplements
Phytoestrogen	intake of 7 specific compounds and total phytoestrogens

Odds ratios and 95% confidence intervals are presented by race/ethnicity for the above variables, with more detailed background information and analyses provided for the newly hypothesized factors listed above.

Given the paucity of data on breast cancer risk factors in African-American and Latina women, we compare our findings based on cases diagnosed from 1995-1998 to those from two similar population-based case-control studies, namely the Carolina Breast Cancer Study that included White and African-American cases diagnosed from 1993-1996 [Moorman 2000, Hall 2000, Kinney 2000, Moorman 2001] and the New Mexico Women's Health Study that included White and Hispanic cases diagnosed from 1992-1994 [Gilliland 1998, Li 2001, Gilliland 2001].

2.2.4. Demographic and personal characteristics (Tables 2 and 3)

Country of birth: Migrant studies have long noted a higher incidence or mortality from certain cancers among migrants who moved from low to high risk countries [Haenszel 1982, Thomas 1996]. Higher incidence or mortality from breast cancer has been reported in US migrant populations such as Asians [Buell 1973, Haenszel 1968, Locke 1980, King 1980, Stanford 1995] and Hispanics [Menck 1975, Shimizu 1991] compared to the respective populations residing in Asian or Latin American countries. An analysis by birthplace found a 50% lower incidence of breast cancer among foreign-born Hispanics compared to US-born Hispanics [Menck 1975].

Magnitude of association: Among White women, breast cancer risk was not associated with country of birth (OR=1.02). Risk was reduced among both Latinas (OR=0.63) and African-Americans (OR=0.63), though the latter included a very small number of foreign-borns. Among Latinas, we found a significantly lower risk of breast cancer among foreign-born women (age-adjusted OR=0.46). Adjustment for other risk factors diminished the risk reduction somewhat (OR=0.63), but a significantly reduced risk remained, suggesting that the standard risk factors for breast cancer do not explain the difference in risk. Thus country of birth represents other important risk factors yet to be identified. An in-depth analysis of migration and acculturation and breast cancer risk in Latinas has been completed as part of the NCI-funded component of this study.

Prevalence: In our case-control study, 68% of Latina controls were foreign-born, compared to 3% among African-Americans and 9% among Whites. This difference in the prevalence of foreign-born women predicts a lower incidence of breast cancer in Latinas.

Education: Many previous studies have reported a higher risk of breast cancer among more educated women [Kelsey 1993a]. The higher risk in more educated women is generally attributed to reproductive characteristics among such women that increase risk (i.e., higher nulliparity, lower parity, later age at first birth). However, even after adjustment for such factors, positive associations with education remain.

Magnitude of association: High age-adjusted odds ratios were observed among Latinas (college graduates: OR=2.86). After adjustment for other risk factors, only a slightly increased risk remained (OR=1.32). The association was similarly weak among Whites (OR=1.27). Among African-Americans, education was not associated with breast cancer risk.

Prevalence: In our multiethnic population, there was a wide range of highest educational level attained. Controls with a high school or higher education accounted for 9%, 18%, and 40% of

Latinas, African-Americans, and Whites, respectively. This trend in educational level parallels the trend in incidence rates of breast cancer (i.e., low rates among Latinas, intermediate rates among African-Americans, high rates among Whites).

Family history of breast cancer: A positive family of breast cancer has been associated with increased breast cancer risk in many studies, and is considered one of the established risk factors for breast cancer. Women with a first-degree relative diagnosed with breast or ovarian cancer have a 2-3 fold increased risk of developing breast cancer [Kelsey 1990; Eby 1994; Pharoah 1997], although risk is substantially higher for women with multiple affected first-degree relatives and/or relatives diagnosed at a young age [Thompson 1994].

Magnitude of association: Odds ratios associated with family history of breast cancer in first-degree relatives varied between racial/ethnic groups (L: OR=1.83, AA: OR=1.10, W: OR=1.34). The lack of association in African-Americans is not consistent with other epidemiologic evidence. In the New Mexico case-control study, the odds ratio for Latinas was 1.4 [Li 2001].

Prevalence: The proportion of controls who reported a positive family history of breast cancer in first-degree relatives varied greatly among the three racial/ethnic groups (L: 7%, AA: 14%, W: 16%), and parallels their incidence rates. Among Latinas, the proportions were 10% among US-born and 5% among foreign-born women. We do not know whether Latinas, particularly foreign-borns, under-reported positive family histories. However, in the New Mexico study, 9.3% of Latinas reported a positive family history in first-degree relatives [Li 2001], which is similar to our finding. In contrast, only 1.7% of controls participating in a case-control study in Mexico City reported a positive family history of breast cancer [Romieu 1996].

Biopsy for benign breast disease: Benign breast disease identified in breast biopsies include a wide spectrum of benign conditions often grouped together as fibrocystic disease, and are identified primarily in premenopausal women [Bodian 1993]. Proliferative disease without atypia and atypical hyperplasia are both associated with increased risk.

Exposure assessment: We assessed in the questionnaire whether the study participant ever had a biopsy for benign breast disease and age at biopsy. Since many women are diagnosed following a biopsy, we restricted positive reports of biopsies for benign breast disease to those biopsies that were performed at least 2 years prior to diagnosis (cases) or selection into the study (controls).

Magnitude of association: We found slightly increased odds ratios that were similar across the three racial/ethnic groups, though slightly higher in Whites (L: OR=1.11, AA: OR=1.19, W: OR=1.36).

Prevalence: The proportion of controls reporting a prior breast biopsy ranged from 12-19% across the three racial/ethnic groups (L: 12%, AA: 17%, W: 19%), paralleling the incidence rates of breast cancer. Among US-born Latinas, the proportion (17%) was similar to that of Whites and African-Americans, but notably higher than the proportion among foreign-born Latinas (9%).

2.2.5. Menstrual factors (Tables 4 and 5)

Menstrual factors have been consistently associated with breast cancer risk, suggesting an important etiologic role for ovarian hormones. Risk is increased in women with young age at

menarche and late age at menopause. Risk is reduced by about 50% following bilateral oophorectomy before age 40, compared to natural menopause, and is thought to be due to the decline in ovarian hormones following surgery. Hysterectomy alone does not appear to be associated with breast cancer risk [Kelsey 1993b]. Between menarche and menopause, a woman is exposed to significant levels of reproductive hormones, which decrease greatly after menopause. Thus, longer duration of exposure to sex hormones during the reproductive years appears to increase breast cancer risk [Kelsey 1993b].

Age at menarche:

Magnitude of association: Consistent with the epidemiologic literature, late age at menarche (age 14 or older) was associated with decreased risk of breast cancer, with similar odds ratios found for the three racial/ethnic groups (L: OR=0.64, AA: OR=0.83, W: OR=0.72). In contrast, Gilliland [1998] found no association with age at menarche among Hispanics (OR=1.11).

Prevalence: Onset of first menstruation at age 14 or later was more frequently reported by Latinas (33%) than African-Americans (28%) and Whites (25%). Among US-born Latinas, the percentage (23%) was similar to that for Whites and African-Americans, but considerably lower compared to foreign-born Latinas (38%). Age at menarche before age 12 was reported by similar proportions of women in the three groups (L: 21%, AA: 21% of African-Americans, W: 20%). The difference in late age at menarche is consistent with the observed incidence rates in the three racial/ethnic groups.

Menopausal status and type of menopause:

Determination of menopausal status: Women were considered postmenopausal if their periods had stopped more than 1 year prior to diagnosis/selection and they had never used hormone replacement therapy (HRT) or used HRT only after the cessation of menstruation. Also included in this group were women who began using HRT prior to the cessation of menses but had attained age 55 or older at the time of diagnosis/selection, and women who reported a bilateral oophorectomy and/or hysterectomy. Women who had begun using HRT prior to the cessation of menses but had not attained age 55 were excluded from these analyses as their menopausal/ovarian status could not be determined. The remainder of women were considered premenopausal.

Magnitude of association: Compared to premenopausal women, postmenopausal women had a lower risk of breast cancer in all three racial/ethnic groups (L: OR=0.78, AA: OR=0.74, W: OR=0.86). Comparing women with natural and surgical menopause (i.e., hysterectomy, or bi-lateral oophorectomy), we found that among Latinas surgical menopause was associated with a slightly increased risk of breast cancer (OR=1.36). Slightly reduced risks were observed among African-Americans (OR=0.78) and Whites (OR=0.80).

Prevalence: Surgical menopause was more frequently reported by African-Americans (54%) than Whites (39%) or Latinas (33%).

Age at menopause:

Determination of age at menopause: Among postmenopausal women, age at menopause was the age at last menstruation among those with natural menopause, and age at surgery for

those with surgical menopause (i.e., bilateral oophorectomy and/or hysterectomy). Women aged 55 and older who started using HRT prior to cessation of menstruation were classified as postmenopausal with unknown age at menopause.

Magnitude of association: Consistent with previous reports [Kelsey 1993b], we noted 2-3 fold increased risks among Latinas (OR=3.96) and Whites (OR=2.66) with natural menopause after age 54, compared to natural menopause before age 45. In contrast, among naturally menopausal African-American women, risk decreased with increasing age at menopause. Among Latinas and African-Americans, age at surgical menopause was not associated with risk. Whites with surgical menopause after age 44 had a slightly increased risk (OR=1.46).

Prevalence: Natural menopause before age 45 was almost twice as common among Latinas (23%) compared to Whites (10%) which is consistent with the observed incidence patterns. Menopause after age 54, however, was most frequently reported by African-Americans (25%), followed by Whites (13%) and Latinas (7%).

2.2.6. Reproductive factors (Tables 6 and 7)

Reproductive factors have been consistently associated with the risk of breast cancer. Risk is increased among nulliparous women and those with late age at first pregnancy, and risk decreases with increasing parity [Kelsey 1993b]. The first pregnancy presumably is associated with terminal differentiation of breast cells and reduced risk of subsequent DNA damage. Alternatively, cell cycle following the first pregnancy may be longer, allowing more time for DNA repair [Colditz 1995]. Thus, reproductive events are thought to influence the rate of growth of breast cells and the accumulation of DNA damage.

Exposure assessment: Our questionnaire included a complete pregnancy history that inquired about each pregnancy (i.e., outcome of pregnancy, date of outcome, and length of pregnancy). From this information we derived the pregnancy variables, including nulliparity, parity, and age at first full-term pregnancy.

Nulliparity:

Magnitude of association: Compared to parous women with 1 or 2 full-term pregnancies, we found slightly increased risks of breast cancer among nulliparous Latinas (OR=1.33) and African-Americans (OR=1.30), but not among Whites (OR=0.93). The odds ratios for US- and foreign-born Latinas were 0.93 and 2.20, respectively (data not shown). The findings by Gilliland [1998] are similar to ours: odds ratios associated with nulliparity (compared to parity 1) were 2.75 for Latinas and 0.99 for Whites. In older studies among mostly White women, odds ratios associated with nulliparity ranged from 1.2 to 1.7 [Kelsey 1993b]. The increased risk in nulliparous women may in part be related to infertility and related hormonal problems. The large majority of studies, however, found no relationship between infertility and breast cancer risk [Weiss 1998].

Prevalence: In our study, the proportion of nulliparous controls varied greatly by race/ethnicity (L: 6%, AA: 11%, W: 19%). Big differences were also observed between US- and foreign-born Latinas (9% and 4%, respectively). This wide range in nulliparity (4% - 19%) suggests, that the reasons for nulliparity (i.e., infertility vs. childless by choice) may vary across populations. The small proportion of nulliparous women among Latinas may largely represent

women with infertility problems which may increase their risk of breast cancer. In contrast, the large proportion of nulliparous women among Whites is likely to include many women who are nulliparous by choice, which may not increase their risk of breast cancer.

Age at first full-term pregnancy:

Magnitude of association: Among Latinas, age-adjusted odds ratios increased with increasing age at first full-term pregnancy. For the first full-term pregnancy at age 30 or later the odds ratio was 1.65. Adjustment for other risk factors, including parity, reduced the odds ratio to 1.03, although slightly increased odds ratios remained for the first pregnancy at ages 20-24 (OR=1.20) and 25-29 (OR=1.23). Among African-Americans, risk was increased only for a first pregnancy at age 30 or later (OR=1.31). Risk among Whites decreased slightly with increasing age at first pregnancy, and was lowest for the first pregnancy at age 30 or later (OR=0.60).

Our findings do not agree with those reported by Gilliland [1998] who found an increase in risk with increasing age at first full-term pregnancy among both Latina and White women. Previous studies in mostly White women generally reported positive associations with age at first full-term pregnancy. In the CASH study, a case-control study of mostly White women under age 55, the odds ratio (adjusted for other risk factors, including parity) was 1.6 for first pregnancy at age 35 or later relative to first pregnancy before age 18 [Layde 1989].

Interestingly, a large case-control study of breast cancer in women under age 55 found no association with age at first birth among women without fertility problems. Among women with self-reported fertility problems, a three-fold increased risk was associated with first birth at age 35 or older [Weiss 1998]. This finding suggests that the increased risk associated with late age at first pregnancy may be partly attributable to fertility problems. In our questionnaire we did not assess fertility problems. We are therefore not able to evaluate whether the lack of association with nulliparity and late age at first birth among Whites is explained by a relatively large proportion of women who are childless or delayed pregnancy by choice. In older studies, the proportion of women who were nulliparous or had their first pregnancy at a late age tended to be much smaller and may have included many more women with fertility problems.

Prevalence: Among parous women, a first full-term pregnancy at age 30 or later was more common among Whites (18%) than Latinas (12%) and African-Americans (7%). This reproductive pattern predicts a higher incidence rate among African-Americans than Latinas. A first full-term pregnancy before age 20 was 3-4 times more common among African-Americans (37%) and Latinas (29%) compared to Whites (10%). This difference also predicts the highest incidence rate among African-Americans.

Parity:

Magnitude of association: Among Latinas, there was a trend of decreasing risk with increasing number of full-term pregnancies. Parity of 5 or more full-term pregnancy was associated with a significant risk reduction (OR=0.54). Contrary to the epidemiologic literature, we found no clear trends with parity among African-Americans and Whites, and parity of 5 or higher was not associated with reduced risks in these populations (A: OR=0.90, W: OR=1.06). Gilliland [1998] found a reduction in risk among White women (OR=0.70) with 4 or more full-term pregnancies, but not among Latinas (OR=1.27).

Prevalence: The proportion of controls with 5 or more full-term pregnancies was considerably higher in Latinas (30%) than African-Americans (16%) and Whites (7%). This difference is consistent with the observed incidence rates.

2.2.7. Breast-feeding (Tables 8-10)

In the mid-1990s, when this case-control study was funded by NCI and DOD, the epidemiologic literature on the relation between breast-feeding and breast cancer risk was inconsistent [Kelsey 1993]. Most of the older studies, particularly a large international case-control study by MacMahon [1970], did not find an association with breast-feeding. In the early 1990s, however, new evidence emerged that suggested a protective effect associated with long cumulative duration of breast-feeding. Based on a recent review of this topic [Lipworth 2000], it appears that long cumulative duration of breast-feeding may indeed reduce breast cancer risk, and that a protective effect may be stronger in or limited to premenopausal women or women under age 40. The epidemiologic evidence, however, is not consistent and some of the recent studies failed to detect a risk reduction.

The strongest evidence stems from Asian populations who more commonly breast-feed for very long periods of time than Western populations. Substantial risk reductions have been reported for Chinese women who breast-fed for many years. Compared to women who breast-fed for less than three years, the odds ratios were around 0.4 to 0.5 for women who breast-fed for ten years or longer [Yuan 1988, Tao 1988, Wang 1992]. This raises the possibility that the prevalence of prolonged lactation in Western populations may be too low to detect a protective effect. We were particularly interested in assessing the effect of breast-feeding in Latina women who have a higher prevalence of breast-feeding than other US populations. Strong reductions in risk with increasing duration of breast-feeding were observed in both pre- and postmenopausal women from Mexico City [Romieu 1996].

Exposure assessment: The questionnaire included a complete pregnancy history that inquired about breast-feeding practices in relation to each live birth.

Magnitude of association among premenopausal women: A history of breast-feeding was associated with reduced breast cancer risk among Whites only (0.72). There was no association among Latinas (OR=1.00) or African-Americans (OR=0.93). Among Latinas, lifetime breast-feeding of 12 months or longer was associated with an age-adjusted odds ratio of 0.67. Adjustment for other risk factors, however, eliminated a protective effect (OR=1.13). Among African-Americans and Whites, adjustment for other risk factors changed the odds ratios only slightly. For lifetime breast-feeding of 12 months or longer, the odds ratios were 0.76 and 0.37, respectively. These findings differ from those reported by Gilliland [1998]. In the New Mexico Health Study both premenopausal Latinas and Whites who breast-feed for 13 months or longer had reduced risks of breast cancer (OR=0.41 and OR=0.63, respectively).

Hypothesizing that the lack of ovulation during breast-feeding may be the underlying biologic mechanism, we limited the exposure to exclusive breast-feeding (i.e., breast-feeding without supplemental food). For exclusive breast-feeding for 6 months or longer, we found odds ratio of 0.59 and 0.45 for African-Americans and Whites, respectively.

Average breast-feeding per child for 6 months or longer reduced risk among African-Americans (OR=0.69) and Whites (OR=0.45), but not among Latinas. Breast-feeding of three or

more children was associated with odds ratios of 0.60 among African-Americans and 0.26 among Whites. Use of medication to stop milk production increased risk among Latinas (OR=1.62) and Whites (OR=2.19), but not among African-Americans (OR=0.81).

The interpretation of these results is limited by the relatively small sample size of premenopausal women included in this study. None of the results were statistically significant. Our results suggest a protective effect among African-American and White women only. Separate analyses (data not shown) reveal a protective effect for breast-feeding of 12 months or longer among US-born Latinas (OR=0.67) that is similar to that found for African-Americans (0.76) and Whites (0.37). Among foreign-born Latinas, breast-feeding was associated with a nearly three-fold increased risk. That analysis was based on very small numbers of women who did not breast-feed (8 cases and 24 controls, or 12% of cases and 17% of controls).

Given the limited number of premenopausal women included in this study, it is difficult to evaluate what aspect of breast-feeding may be etiologically most relevant, namely the overall duration of breast-feeding, the duration of exclusive breast-feeding, the average duration of breast-feeding per child, or the number of children breast-fed.

Magnitude of association among postmenopausal women: A history of breast-feeding reduced breast cancer risk among all three racial/ethnic groups, with odds ratios of 0.76, 0.85, and 0.89 among Latinas, African-Americans, and Whites, respectively. There was a trend of decreasing risk with increasing duration of breast-feeding among Latinas, but not among African-Americans. Among Whites, risk was reduced only among those who breast-fed for 12 months or longer. There was no risk reduction among those who breast-fed for shorter periods of time. As for premenopausal women, our findings for Latinas differ from those reported by Gilliland [1998] who found no risk reduction among postmenopausal Latinas (OR=1.25). Similar to our study, risk was reduced among postmenopausal White women who breast-fed for 13 months or longer (OR=0.34).

Odds ratios for average breast-feeding per child of 6 months or longer were similar across the three racial-ethnic groups (L: OR=0.70, AA: OR=0.84, W: OR=0.73). For breast-feeding of 3 or more children, the odds ratios were 0.80, 0.89, and 0.68 among Latinas, African-Americans, and Whites, respectively. Use of medication to stop milk production significantly increased risk among Whites (OR=1.54), but not among Latinas or African-Americans.

Except for the last cited odds ratio, none of our results were statistically significant, but the magnitude of associations were similar across racial/ethnic groups. Among Latinas, lifetime duration of breast-feeding was most strongly associated with breast cancer risk. Among Whites, the number of children was the best predictor of risk. Among African-Americans, all breast-feeding variables were only weakly associated with risk.

Prevalence: The proportion of prermenopausal controls who breast-fed for 12 months or longer was similar among Whites (47%) and Latinas (45%), and considerably lower among African-Americans (19%). The effect of this difference would be to increase the incidence rate among African-Americans. Similar incidence rates would be expected among Whites and Latinas.

Among postmenopausal controls, breast-feeding for 12 months or longer was reported by 46% of Latinas, 24% of African-Americans, and 23% of Whites. This difference would predict a lower incidence among Latinas and similar incidence among African-Americans and Whites.

2.2.8. Exogenous hormones (Tables 11 and 12)

Oral contraceptives (OC): A very large international collaborative re-analysis found a small increase in current and recent (within 4 years of diagnosis) users of OC (OR=1.24) [Collaborative Group 1996]. But there was no increased risk among those who stopped using Oc 10 or more years prior to diagnosis. Risk was not associated with duration of OC use.

Magnitude of association: Consistent with other studies, oral contraceptive use was not associated with breast cancer risk in our study. In any of the three racial/ethnic groups risk was not increased among those who used oral contraceptives for 5 years or longer. This finding is consistent with the Carolina Breast Cancer Study that found no association among African-American and White women aged 50 and older [Moorman 2001]. A small but insignificant increase in risk was noted among both African-American and White women under age 50. It is therefore unlikely that OC use explains the racial/ethnic differences in breast cancer incidence.

Prevalence: About one third of African-American and White controls reported use of oral contraceptives for 5 years or longer. Among Latinas, this percentage was slightly lower (21%).

Hormone replacement therapy (HRT): A collaborative re-analysis of original data from 51 epidemiologic studies indicates that an increased risk of breast cancer is limited to current HRT users, among whom risk increases with increasing duration of use [Collaborative Group 1997]. For current users who used hormones for 5 years or longer, risk was significantly increased by 35% compared with never users. Women who stopped HRT more than 5 years previously had no increased risk, regardless of duration of use.

In most of the older studies, estrogen without progestin (unopposed estrogen) was taken. Widespread use of unopposed estrogen replacement therapy (ERT) began in the United States in the 1960s and peaked in 1974, and declined following the first reports published in 1975 that linked ERT to 5-10 fold increased risks of endometrial cancer [Ross 2000]. Though the addition of progestin to estrogen reduced the risk of endometrial cancer, recent epidemiologic data, including the collaborative analysis, suggest that use of estrogen plus progestin is associated with a higher risk of breast cancer than use of unopposed estrogen [Collaborative Group 1997, Colditz 1995, Colditz 1998, Persson 1999, Schairer 2000, Ross 2000]. Data are also emerging that suggest an adverse effect may be stronger in or limited to lean women [Magnusson 1999].

Magnitude of association: In our study, use of menopausal hormones did not increase breast cancer risk in any of the three racial/ethnic groups. Current use was associated with slightly decreased risks in all three groups.

Prevalence: Use of hormone replacement therapy was considerably more common among Whites (60%) than Latinas (37%) and African-Americans (40%). Similarly, current use was higher in Whites than Latinas and African-Americans.

2.2.9. Body size characteristics (Tables 13-15)

Many previous studies reported an increased risk of breast cancer among postmenopausal women with a high body mass index (BMI) [Friedenreich 2001], but the associations seem stronger in case-control than cohort data [Hunter 1993]. Obese postmenopausal women have

higher serum estrogen levels, reflecting the conversion of androgens in adipose tissue to estrogen. Obesity is also associated with higher serum levels of testosterone, and lower levels of sex hormone-binding globulin (SHBG), which in turn increase levels of free estrogen. Recent studies suggest that an association with BMI is only observed among postmenopausal women who never used HRT [Franceschi 1996, Huang 1997]. Among those using HRT, risk appears to be decreased, similar to the pattern seen for premenopausal women. Obese premenopausal women have an increased frequency of anovulation, and thus decreased production of progesterone. Leptin levels which increase with obesity, inhibit ovarian estrogen production, thereby contributing to lower breast cancer risk among obese premenopausal women.

Besides BMI, recent studies have evaluated other anthropometric measures, including height (a proxy for childhod and adolescent energy intake), waist-to-hip ratio (a measure of the type of fat deposition), and weight gain. Among premenopausal women, risk increases with increasing height, but is not associated with waist-to-hip ratio. Among postmenopausal women, risk increases with increasing height and waist-to-hip ratio. Weight loss appears to decrease risk [Friedenreich 2001].

Exposure assessment: The interviewers took three measurements of height and two measurements of weight at the time of the interview using a standardized scale and stadiometer. The measurements were averaged to compute the body mass index (BMI) as an index of body size (weight in kilograms divided by the square of height in meters). For study participants who declined the anthropometric measurements, information on self-reported height and weight was used. We used the definition by the WHO to classify individuals as underweight (BMI < 18.5), normal weight (BMI=18.5-25), overweight (BMI=25.1-30.0) and obese (BMI >30).The interviewers also took three measurements of waist and hip circumferences which were averaged to compute the waist-to-hip ratio (WHR), a measure of central adiposity. Lifetime weight gain was estimated as the difference between the lowest and highest weight between age 25 and reference age.

Magnitude of association among premenopausal women: Consistent with other reports, we noted an increase in risk with increasing height among premenopausal women. This association was strongest among Whites, with an odds ratio of 2.83 for women ≥164 cm relative to those <157 cm. The increase in risk was less pronounced in African-Americans (OR=1.39 for height ≥164 cm). Among Latinas, adjustment for other risk factors greatly weakened the association with height. Further analysis (data not shown) by country of birth revealed that an association with height was limited to US-born Latinas (OR=1.78 for height ≥164 cm). No association was found among foreign-born Latinas. Similarly, the Carolina Breast Cancer Study found a positive association with height among African-American women (OR=2.93 for >165 cm vs. ≤160), although no association was found among White women [Hall 2000].

In all three racial/ethnic groups, risk decreased with increasing BMI, though the risk reduction was smallest among African-American women (OR=0.80 for highest BMI). Similarly, the Carolina study found a weaker effect among African-Americans (OR=0.89 for highest BMI) [Hall 2000]. Hall [2000] speculated that the group of premenopausal women included a relatively large number of young African-American women with surgical menopause. When they repeated the analysis for women under age 50, they found a considerably greater risk reduction for African-Americans (OR=0.50 for highest tertile).

A high waist-to-hip ratio (that is, central or abdominal adiposity) was associated with decreased risk among Latinas (OR=0.69) and Whites (OR=0.53). Among African-Americans,

those with intermediate waist-to-hip ratio had a decreased risk (OR=0.76), but not those with a high ratio (OR=0.98). Our findings are not in agreement with the Carolina study which found two-fold increased risk among both African-American and White women with a high waist-to-hip ratio [Hall 2000].

High lifetime weight gain was associated with reduced risk among Whites (OR=0.39) and African-Americans (OR=0.60), but not among Latinas (OR=1.29). The effect of weight gain was not evaluated in the Carolina study [Hall 2000].

Prevalence among premenopausal controls: The proportions of several body size characteristics were highest among African-American women. Height exceeding 164 cm (highest tertile among all controls combined) was more common among African-Americans (53%) and Whites (48%) than among Latinas (14%). This distribution would predict the highest incidence rate among African-Americans. The proportion of overweight women was considerably higher among African-Americans (52%) and Latinas (43%) than Whites (28%). Similarly, a high waist-to-hip ratio (highest tertile among all controls combined), was more common among African-Americans (44%) and Latinas (38%) than Whites (14%). Twice as many African-Americans (55%) reported a weight gain since age 25 of more than 21 kg compared to Latinas (29%) and Whites (27%). These differences would predict lower incidence rates among African-Americans and Latinas compared to Whites.

Magnitude of association among postmenopausal women: Among postmenopausal women, risk increased with increasing height, with similar odds ratios observed in the three racial/ethnic groups (ranging from 1.27 to 1.41 for the highest tertile). In the Carolina Study, height was positively associated with height among Whites, but no among African-Americans [Hall 2000].

High BMI was associated with increased risk only in women who never took hormone replacement therapy (HRT). A particularly high risk was seen among Whites, with a significant odds ratio of 3.43 for those with a BMI $\geq$30. Among Latinas and African-Americans, the increases in risk were more modest (OR=1.27 and OR=1.32, respectively). Among women who used HRT, reduced risks associated with high BMI were noted among Latinas and Whites, but an increased risk among African-Americans. In the Carolina study, BMI was not associated with risk among White women, and risk was reduced among African-Americans with high BMI [Hall 2000]. Restricting the analysis to women aged 50 and older who never used HRT revealed a 3-fold increased risk among Whites, but no association among African-Americans. Thus, the association with BMI in Whites is similar in the two studies. Hall [2000] speculated that the lack of association with BMI in postmenopausal African-American women may be due to their high prevalence of estrogen receptor-negative breast tumors.

Associations with waist-to-hip ratio and weight gain were less consistent across racial/ethnic groups. A high waist-to-hip ratio slightly increased risk among Latinas (OR=1.28), but was not associated with risk among African-Americans and Whites. Stronger effects were reported for African-Americans (OR=1.62) and Whites (OR=1.64) in the Carolina study [Hall 2000]. Weight gain since age 25 was only weakly associated with risk in Latinas (OR=1.27) and Whites (OR=1.13). There was no association among African-Americans.

Prevalence among premenopausal controls: The proportion of women who were tall or overweight, or had a high waist-to-hip ratio or large weight gain was highest among African-Americans which would predict the highest incidence in this group. Latinas had the lowest

proportion of tall controls, but greater proportions of controls with high BMI and waist-to-hip ratio than Whites. The distribution of these anthropometric measures is therefore not consistent with the observed incidence rates among the three populations.

2.2.10. Dietary factors (Tables 16 and 17)

Despite a large number of epidemiologic studies, the relation between diet and breast cancer risk remains inconclusive [World Cancer Research Fund 1997]. A number of dietary factors have been hypothesized to increase risk, including total caloric intake, fat, specific fatty acids, meat, and alcohol. Except for alcohol, the evidence on dietary factors remains largely inconsistent. Dietary factors hypothesized to reduce risk include fruits, vegetables, phytoestrogens, and specific vitamins. We report here on five selected dietary factors (total caloric intake, fat, alcohol, vitamin D, and phytoestrogens).

Exposure assessment: We estimated daily intake of calories, fat, and alcohol from the food frequency questionnaire that inquired about usual food and beverage consumption during the reference year in terms of frequency of consumption and serving size.

Caloric intake:

A number of studies have shown that diets high in total calories increase breast cancer risk [World Cancer Research Fund 1997]. This effect is likely to operate via weight gain and obesity.

Magnitude of association: High caloric intake (2357 or more calories per day) slightly increased breast cancer risk among African-Americans (OR=1.37) and Latinas (OR=1.23), but not among Whites (OR=0.87).

Prevalence: High caloric intake (highest tertile among all controls combined) was more prevalent among Latinas (45%) than African-Americans (29%) and Whites (22%), and would predict the highest incidence rate among Latinas.

Fat intake:

Dietary fat has been the focus of many epidemiologic studies [Lee 2000]. The data remain inconclusive, however. A meta-analysis of prospective studies found no association [Hunter 1996], whereas meta-analyses of case-control studies found positive associations [Howe 1990, Boyd 1993]. Consideration of specific fatty acids and age at exposure may contribute towards a better understanding of the relation between dietary fat and breast cancer risk [Hunter 1999].

Magnitude of association: Fat intake during the reference year was not consistently associated with breast cancer risk in the three racial/ethnic groups. High fat intake increased risk among African-Americans (OR=1.60) and Latinas (OR=1.21), but not among Whites (OR=0.97). Our study was not designed to assess the effect of diet during other periods of life (e.g., childhood or adolescence).

Prevalence: High fat intake was more prevalent among African-Americans (37%) and Latinas (35%) than Whites (28%). This difference would predict higher incidence rates in African-Americans and Latinas.

2.2.11. Alcohol consumption (Tables 16 and 17):

A large body of evidence suggests that even moderate alcohol consumption increases breast cancer risk [Rosenberg 1993, Longnecker 1994, Smith-Warner 1998, Ellison 2001]. Two meta-analyses estimated that daily consumption of one alcoholic drink increases risk by about 10% [Longnecker 1994, Ellison 2001]. The proportion of heavy drinkers, however, was small in most studies conducted in the U.S. where alcohol intake is generally low (on average, less than one drink per day) [Zhang 1999]. An increase in risk may be related to drinking at a young age. The epidemiologic evidence, however, is not consistent. It has been suggested that average lifetime alcohol consumption may be the best predictor of risk [Longnecker 1995; Longnecker 1995b]. The association with alcohol consumption may be stronger among younger or premenopausal women [Howe 1991; Ferraroni 1998], but there is no consistent evidence of effect modification by menopausal status [Rosenberg 1993, Longnecker 1994, Schatzkin 1994].

Magnitude of association: Daily consumption of 10 or more grams of alcohol (one or more alcoholic drink per day) was only weakly associated with breast cancer risk in our study (L: OR=1.11, AA: OR=1.22, W: OR=1.30). Similarly, both the Carolina Study [Kinney 2000] and the New Mexico Study [Baumgartner 2000] found little evidence of an association among African-American, Latina, and White women. We collected no information on lifetime alcohol consumption and therefore could not assess the cumulative effect of alcohol consumption, or the effect of alcohol consumption during specific periods of life.

Prevalence: The proportion of controls with a daily consumption of 10 or more grams of alcohol was considerably higher among Whites (19%) than African-Americans (10%) and Latinas (5%). The distribution of this risk factor is consistent with the observed incidence rates.

2.2.12. Physical activity (Tables 18-24)

Since the first epidemiologic study published in 1985 by Frisch and colleagues (Frisch 1985), that reported a lower risk of breast cancer among former college athletes, over 35 studies have addressed this potentially modifiable lifestyle factor. Several reviews on the epidemiologic evidence have been published in the last few years (Gammon 1998; Friedenreich 1998; McTiernan 1998, Friedenreich 2001), and many studies addressing this issue have been published since we received funding in 1995 to test this hypothesis in Hispanic women. As summarized by Friedenreich [2001], 23 of 35 studies conducted to date reported a decreased risk among the physically most active women, with risk reductions of up to 70% and dose-response trends found in some studies. The current epidemiologic data suggest that high physical activity may confer a greater reduction in breast cancer risk among premenopausal than postmenopausal women.

The epidemiologic evidence, however, is not consistent. The magnitude of risk reductions varies across studies and is difficult to evaluate because many different approaches have been used to assess physical activity. Some studies assessed sports and exercise only, others focused on occupational physical activity, and or assessed physical activity at a single point in life. Except for a recent case-control study published by Friedenreich [2001], no previous study has performed a comprehensive assessment of lifetime physical activity from all sources, including exercise and sports, transportation, household chores, and occupations. It is not known to what extent the incomplete assessment of physical activity from all sources contributed to some of the discrepant

results. Most studies conducted to date included White women [McTiernan 2000]. It is not known whether the influence of physical activity on breast cancer risk differs among racial/ethnic groups.

Exposure assessment: We focused our assessment of physical activity on lifetime physical activities from multiple sources, including sports and exercise, transportation, strenuous household chores, and jobs. Using a set of questions developed by Bernstein et al. [Bernstein 1994], we assessed a lifetime history of regular participation (at least 1 hour per week for at least 4 months out of the year) in sports and exercise, and recorded the name of the activity, the ages when the activity started and ended, the number of hours per week and the number of months per year the study participant engaged in the activity. We presented show cards to participants listing examples of vigorous and moderate exercise activities. Participants were asked to report all regular sports and exercise activities, including those not listed on the show cards.

We developed a similar format of questions (i.e., age started, age ended, hours per week, months per year) to assess lifetime histories of physical activity from transportation and daily living. These questions preceded the lifetime exercise history, and inquired about regular (at least 20 minutes per day for at least 4 months out of the year) walking and bicycling to school and work, and regular (at least 2 hours per week for at least 4 months out of the year) strenuous outdoor and household chores. We limited the assessment to strenuous chores since recall is more reliable for strenuous activities compared to light activities [Friedenreich 1998]. The interviewers presented a show card of examples of strenuous outdoor chores, including farm work, yard work and other strenuous chores such as bailing hay, picking fruit, digging, mowing the lawn, chopping wood, shoveling snow, carrying water from the river, washing clothes with a washboard, and grinding corn. Examples of strenuous household chores included scrubbing floors, sweeping, vacuuming, and washing windows. Study participants were asked to include regular strenuous chores not listed on the show cards, and to include only chores they did for themselves or their family and were not paid for, since we assessed paid work in the occupational history. The lifetime histories of walking and bicycling to work or school and strenuous outdoor and household chores included as many episodes of activity as the participant reported.

Lastly, we assessed occupational physical activity through a lifetime occupational history. For each job held at least one year, we recorded job title and type of business or industry, ages when job started and ended, number of hours worked per week, and self-assessed level of physical activity (i.e., mostly sitting, mostly standing or walking, mostly moderate physical activities, mostly strenuous activities or hard labor).

Exposure variables: For each source of physical activity (i.e., exercise, transportation, chores, jobs) we estimated the average lifetime number of hours spent per week per year by summing the weekly hours of activity and dividing by the number of years between menarche and reference year. For occupational physical activity, we summed the weekly number of hours worked in jobs that the participant identified as mostly moderately active or mostly strenuous or hard labor. For exercise and sports activities, we assigned a metabolic equivalent of energy expenditure (MET) score to each reported activity using the compendium by Ainsworth [1993] and multiplied the MET score by the hours per week spent in that activity to estimate MET-hours for each episode of activity. Summing the MET-hours across all reported episodes of activity, we estimated the average MET-hours between menarche and reference year.

We calculated two measures of total physical activity. We estimated average lifetime total activity by summing the average weekly hours for each of the four sources of activity. To consider

intensity of activity, we estimated average MET-hours of total activity by summing the MET-hours for each type of activity. The MET scores we assigned to specific activities were 3.5 for walking, 6.0 for bicycling, 6.0 for strenuous outdoor chores, 5.0 for strenuous household chores, 4.0 for moderately active jobs, and 6.0 for strenuous jobs.

Because the underlying biologic mechanism may be different for pre- and postmenopausal women, we performed separate analyses by menopausal status.

Magnitude of association among premenopausal women (Table 18):

Exercise and sports: Among whites, 5.6% of controls never exercised during their lifetime (i.e., at least 1 hour per week for 4 months out of the year). The proportions were considerably higher among African-Americans (15.6%) and Latinas (31.1%). Given the small proportion among Whites, we included in our reference group women with a lifetime average of less than 0.5 hours spent in exercise and sports. Spending 4 or more hours per week in exercise reduced risk only among Latinas (OR=0.87). Increased risks were found among African-Americans (OR=1.95) and Whites (OR=1.47). Alternative exposure cut points (i.e., <1.5 hrs, 1.5-3.9 hrs, ≥4.0 hrs) produced slightly different results. Risk was decreased among the most active Latinas (OR=0.76) and Whites (OR=0.79), but increased among African-Americans (OR=1.37). Latinas who spent 12 or more years exercising for 4 or more hours per week had an odds ratio of 0.66. A sightly reduced risk was also noted among Whites (OR=0.81), but not among African-Americans (OR=1.57).

Thus, our findings are not in agreement with a case-control study by Bernstein [1994] who reported an odds ratio of 0.42 (CI=0.27-0.64) for Whites under age 40 with a lifetime average of 3.8 or more hours of exercise per week relative to women who never exercised. In that study, 28% of controls never exercised (i.e., at least 2 hours per week), which is considerably higher than the proportion found in our study for Whites (5.6%). However, our minimum activity level for inclusion in the exercise history was less stringent (at least 1 hour per week for 4 months out of the year). This study was the impetus for many subsequent study to assess the association between physical activity and breast cancer risk. Friedenreich et al. [2001] who also used the Bernstein method to assess a lifetime exercise history found no association among mostly White women living in Canada.

Walking, bicycling, and strenuous chores: Generally reduced risks were found among women in the highest exposure categories of walking, bicycling, and strenuous chores. For household chores, odds ratios were 0.57 among African-Americans, 0.74 among Latinas, and 0.76 among Whites. In contrast, Friedenreich [2001] found no association with lifetime household chores among premenopausal women.

Non-occupational activity: Summing the hours spent with exercise, walking, bicycling, and strenuous chores, we found risk reductions among Latinas (OR=0.70) and Whites (OR=0.41), but not among African-Americans (OR=1.09). In the New Mexico study by Gilliland [2001], high non-occupational activity (i.e., sports, walking, heavy housework, heavy outside work) during the reference year was associated with decreased risk among Latinas (OR=0.29 for ≥80 MET-hours/week), but not among Whites.

Occupational activity: Compared to women who never worked in a moderate or strenuous job, those who spent a lifetime average of 10 or more hours per week in such jobs had a lower risk

of breast cancer (L: OR=0.87, W: OR=0.87, AA: OR=0.67). Friedenreich [2001] found no association with occupational activity among White Canadian women.

Total physical activity: Summing the hours per week from all types of physical activities, we found that the most active premenopausal women had a lower risk of breast cancer, with similar risk reductions found in the three racial/ethnic groups (L: OR=0.73, AA: OR=0.68, W: OR=0.76). In contrast, Friedenreich [2001] found no association with lifetime physical activity among premenopausal women.

Prevalence among premenopausal women: Premenopausal Latina control women reported a lifetime (i.e., from menarche to reference year) average of 19.9 hours of physical activity per week, compared to 16.9 hours among African-Americans and 16.4 hours among Whites (Table 19). Among Latinas, 10% of these hours were from exercise, 4% from walking or bicycling, 44% from strenuous household chores, 10% from strenuous outdoor chores, and 32% from mostly moderate or strenuous jobs. Latinas reported significantly more time spent with strenuous chores (10.8 hours per week) than African-Americans (6.8 hours per week) and Whites (7.3 hours per week), and significantly less time spent with exercise and sports (1.9 hours per week) than African-Americans (3.3 hours per week) and Whites (3.5 hours per week). Walking, jogging, and aerobics were among the top 5 exercise activities among all three racial/ethnic groups (Table 20). More Whites (31%) and African-Americans (29%) spent four or more hours per week in exercise than Latinas (17%) (Table 21). High physical activity from all sources, however, was more prevalent among Latinas (39%) than African-Americans (29%) and Whites (27%). These data demonstrate that exercise and sports account for only a small portion of overall physical activity in women. They stress the importance of assessing all sources of physical activity when studying the relation between physical activity and breast cancer or other outcomes. The distribution of high lifetime physical activity predicts similar incidence rates among Whites and African-Americans, and lower rates among Latinas.

Magnitude of association among postmenopausal women (Table 22):

Exercise and sports: As we noted above for premenopausal women, very few White postmenopausal controls (6.7%) never exercised during their lifetime (i.e., at least 1 hour per week for at least 4 months out of the year). The proportions were 17.0% for African-Americans and 30.9% for Latinas. We therefore included in our reference group those who exercised less than 0.5 hours per week. Breast cancer risk was not related to lifetime exercise. Similarly, Friedenreich [2001] found no association with lifetime exercise. Another case-control study [Carpenter 1999] that used the Bernstein method to assess a lifetime history of exercise among White postmenopausal women found a strong association with exercise (OR=0.55, CI=0.37-0.83 for the highest quartile of energy expenditure from exercise).

Walking, bicycling, and strenuous chores: We found no association with walking/bicycling and strenuous chores among postmenopausal women. In contrast, Friedenreich [2001] reported a reduction in risk with household chores (OR=0.69, CI=0.49-0.96 for the highest exposure category). In the New Mexico study by Gilliland [2001], high non-occupational activity (i.e., sports, walking, heavy housework, heavy outside work) during the reference year was associated with decreased risk among both Latinas and Whites (OR=0.38 and OR=0.45, respectively, for $\geq$80 MET-hours/week).

Occupational activity: We found risk reductions for women with a lifetime average of 10 or more hours in moderate or strenuous jobs, with similar odds ratios in the three racial/ethnic groups (L: OR=0.68, AA: OR=0.77, W: OR=0.62). Similarly, Friedenreich [2001] found an odds ratio of 0.76 for the most active women.

Total physical activity: Summing all hours spent in physical activity, those in the highest exposure category (highest tertile among all controls combined) had reduced risks that were, however, smaller than those for premenopausal women. Odds ratios were 0.81 for Latinas, 0.71 for African-Americans, and 0.91 for Whites. Analyses by MET-hours of activity produced similar results. Friedenreich [2001] reported an odds ratio of 0.69 (CI=0.51-0.93) for postmenopausal women in the highest exposure category.

Prevalence among postmenopausal women: The physical activity patterns for postmenopausal women were similar to those of premenopausal women. Postmenopausal Latinas spent significantly more time with total physical activity and chores than African-Americans and Whites, and significantly less time with exercise (Table 23). Walking and dancing ranked among the top 5 exercise activities in all three racial/ethnic groups (Table 24). High lifetime physical activity was considerably more prevalent among Latinas (42%) than Whites (24%), and intermediate among African-Americans (33%). The difference in the prevalence of high lifetime physical activity is consistent with the observed incidence rates.

Summary: Overall, our findings support many other studies that reported a lower risk of breast cancer among physically active women. The risk reductions, however, are not as pronounced as those reported by some other studies, and they are similar for pre- and postmenopausal women among Latinas (OR=0.79 and 0.81) and African-Americans (OR=0.72 and 0.71). Among Whites, a reduction in risk was limited to premenopausal women (OR=0.72 and 0.95). Among all women combined the odds ratios for pre- and postmenopausal women were 0.74 and 0.81, respectively. None of the risk estimates, however, are statistically significant. When we stratified the analysis by age at diagnosis, we found significant risk reductions among women under age 50 (OR=0.69, CI=0.49-0.98) and women aged 50 or older (OR=0.79, CI=0.62-0.99) (Tables 33 and 34).

2.2.13. Vitamin D (Tables 25-28)

In 1990, Garland et al. [1990] hypothesized that vitamin D may reduce the risk of breast cancer. The hypothesis was based on correlations between solar radiation and breast cancer mortality rates, as well as experimental findings. *In vitro* studies have demonstrated that 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], the biologically active metabolite of vitamin D, and its analogues inhibit proliferation, stimulate differentiation, and promote death of many types of normal and malignant cells, including breast cells (reviewed in Colston 1997). In laboratory rats, vitamin D analogues were found to prevent the induction of mammary gland tumors [Anzano 1994] and induce the regression of such tumors [Colston 1992a, Colston 1992b]. The effect of $1,25(OH)_2D$ on gene expression is mediated by the vitamin D receptor (VDR), a ligand-activated transcription factor that belongs to the steroid and thyroid hormone receptor family [Zmuda 2000]. Several recent studies reported associations between breast cancer risk and polymorphisms in the VDR gene [reviewed in Zmuda 2000], thus further supporting the hypothesis that vitamin D may play a role in breast carcinogenesis.

Few analytic epidemiologic studies to date have directly assessed the relation between breast cancer risk and vitamin D from diet and sunlight exposure, the latter of which is the major source of vitamin D. The amount of vitamin D produced in the skin following sunlight exposure is dependent on the intensity of ultraviolet radiation which is strongly influenced by geographic latitude, season, and time of day. In Boston (42.2° N) there is no detectable production of previtamin D from November to February. In Edmonton (52° N) the period when no photosynthesis of previtamin D takes place lasts somewhat longer from October to March, whereas in Los Angeles (34° N) and Puerto Rico (18° N), previtamin D is produced throughout the year [Webb 1988]. However, the efficiency of conversion is greater in Puerto Rico than in Los Angeles. Thus, average annual production of previtamin D is positively associated with solar radiation levels. Other factors that affect the production of vitamin D include host factors such as age, melatonin content, and use of sun screen and protective clothing. Thus, vitamin D is a complex exposure variable to assess in epidemiologic studies. In our case-control study, we considered several components, including sunlight exposure, constitutional and behavioral factors, and dietary vitamin D intake.

Sunlight exposure: Mortality rates from breast cancer are higher in the Northeast than in the South of the U.S. [Garland 1990] and are inversely correlated with solar radiation [Garland 1990, Gorham 1989, Gorham 1990, Morabia 1992]. Although the prevalence of breast cancer risk factors varies across regions, it only partly explains the geographic variation in mortality rates [Blot 1977, Sturgeon 1995]. In 1999, Dr. John and colleagues published findings from a cohort analysis using data from the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study [John 1999]. Several measures of sunlight exposure, including physician-reported sunlight exposure, sun-induced skin damage, self-reported sunlight exposure, and residential solar radiation, were associated with reduced breast cancer risk, with relative risks ranging from 0.50 to 0.79.

Low serum levels of $1,25(OH)_2D$ have been associated with increased breast cancer risk [Janowsky 1999], and with disease progression and development of bone metastases [Mawer 1997]. The evidence, however, is not consistent [Hiatt 1998]. In two studies that examined serum levels of 25(OH)D, low levels were not associated with breast cancer risk [Hiatt 1998, Janowsky 1999].

Exposure assessment: Based on questionnaire data and skin pigmentation measurements we defined several sunlight exposure variables. We considered *self-reported sunlight exposure* (i.e., time spent outdoors at ages 10-15, 25-29, and 55-59, estimated average lifetime time spent outdoors (summing time spent walking and bicycling, doing strenuous outdoor chores, exercising outdoors, and working in outdoor jobs), *measured sunlight exposure* using a Minolta Chromameter (i.e., the difference between facultative (sun-exposed) skin pigmentation measured at the forehead and constitutive (non sun-exposed) skin pigmentation measured at the upper inner arm), and *residential solar radiation exposure* (i.e., average lifetime geographic latitude, a correlate of sunlight exposure, derived from the lifetime residential history).

Magnitude of association: We hypothesized that women with more sunlight exposure would have higher vitamin D levels, and therefore would be at decreased risk of breast cancer. Among African-American and White women, time spent outdoors was associated with reduced risk, with the greatest reductions noted for time spent outdoors at age 25-30. Compared to women who spent less than 1 hour per week outdoors, those who spent 7 or more hours per week outdoors had reduced risks (AA: OR=0.55, W: OR=0.65). Among Latinas, these sunlight exposure

measures were associated with slightly increased risk. Lifetime average time spent outdoors showed no consistent patterns of association across the three racial/ethnic groups. No associations were noted among Whites (OR=0.94) and African-Americans (OR=0.89), a significantly increased risk was found among Hispanics (OR=1.56).

The difference between facultative and constitutive skin pigmentation has previously been found to be a valid indicator of *lifetime* sunlight exposure [Lock-Andersen 1998]. Based on our skin pigmentation measurements, we found that Latina and African-American with high lifetime sunlight exposure had slightly decreased risks of breast cancer (L: OR=0.85, AA: OR=0.88). No association was noted among White women.

Consistent with our hypothesis, we found that White women with high lifetime solar radiation (estimated from the residential history) had a slightly reduced risk of breast cancer (OR=0.79). No association was found among African-Americans. A reduction in risk was also observed among Latinas. For high lifetime solar radiation, the odds ratio was 0.41 (CI=0.23-0.72). Latina women with high lifetime solar radiation spent a proportionately large part of their life in Mexico or Central or South America. In a related analysis of migration factors among Latinas, we found that those who spent less than 10 years in the US had an odds ratio of 0.44 (CI=0.25-0.79), a finding that is similar to our association with residential solar radiation exposure. Both analyses controlled for other risk factors, yet the protective effects remained. Most likely, some lifestyle or environmental factor explains the lower risk among Latinas who recently migrated to the US. Residence in Mexico, Central or South America, however, may correlate with other lifestyle factors that protect against breast cancer. We can therefore not necessarily conclude that high solar radiation explains the lower risk of breast cancer among Latinas.

Prevalence: The proportion of controls with a lifetime average of 3 or more hours per week spent outdoors was highest among Whites (43%) and Latinas (39%), and somewhat lower among African-Americans (34%). The proportion of controls with high lifetime sunlight exposure (based on skin pigmentation measurements) was similar among Latinas (25%) and Whites (28%), but considerably lower among African-Americans (9%).

Constitutional and behavioral factors:

Exposure assessment: In the questionnaire, we assessed several factors that influence vitamin D status, including *constitutional factors* (i.e., constitutive skin pigmentation, skin reaction to sun exposure, tanning) and *behavioral factors* (i.e., wearing of protective clothing, staying in the shade, use of sunscreen).

Magnitude of association: We hypothesized that women with lighter natural skin would be at decreased breast cancer risk as vitamin D production decreases with increasing melatonin content, given the same duration of sunlight exposure. In all three racial/ethnic groups, those with lighter skin (measured at the upper inner arm) had a slightly decreased risk of breast cancer (L: OR=0.81, AA: OR=0.81, W: OR=0.70). We further hypothesized that women who did not burn following intense sunlight exposure would spend more time outdoors, than those who developed severe blisters or burns, and thus would be at decreased risk of breast cancer. Similarly, women who develop a deep tan would spent more time outdoors than those who develop no tan. For both variables, we found no associations in the hypothesized direction.

We hypothesized that women who did not protect themselves from sunlight exposure or never used sunscreen would be at decreased risk. We found no associations in the hypothesized direction.

Summary of sun exposure variables: The most consistent associations with sunlight exposure and related variables emerged for White women. Risk was reduced among women who spent a considerable amount of time outdoors at age 25-30 (OR=0.65), lived in areas of high solar radiation (OR=0.79), and had light constitutive skin pigmentation (OR=0.70). These findings are supportive of the hypothesis that vitamin D from sunlight exposure may decrease breast cancer risk.

Among African-Americans and Latinas, the patterns of associations were less consistent. Risk was reduced among African-Americans who spent considerable time outdoors at ages 25-30 (OR=0.55) or 55-59 (OR=0.56), and among those with medium (OR=0.68) or light (OR=0.81) constitutive skin pigmentation. Among Latinas, light constitutive skin pigmentation (OR=0.81), living in areas of high solar radiation (OR=0.41), and high lifetime sunlight exposure based on skin pigmentation measurements (OR=0.85) were the only variables associated with reduced breast cancer risk.

The exposure measure that was most consistently associated with risk is constitutive skin pigmentation. Individuals with lighter skin had lower risks than those with darker skin (W: OR=0.70, AA: OR=0.81, L: 0.85). Skin pigmentation is known to be a major determinant of cutaneous vitamin D synthesis.

Dietary vitamin D: Only a few studies have reported on the association with dietary vitamin D. Data are inconsistent [Simard 1991, Nunez 1996] and difficult to interpret because none of the dietary studies considered vitamin D from sunlight exposure which, for most individuals, is the primary source of vitamin D. In Dr. John's cohort analysis of NHANES I Follow-up data [John 1999], the association with dietary vitamin D assessed by a 24-hour dietary recall was weak. Relative risks were 0.86 (CI=0.59-1.25) for intake of 200 IU or more, and 0.88 (CI=0.60-1.31) for daily use of multivitamins.

Exposure assessment: To assess dietary vitamin D intake, we expanded the food frequency questionnaire to include all major sources of dietary vitamin D (i.e., eggs, liver and liverwurst, fatty fish, milk, margarine, cereal). We then added vitamin D values to the nutrient database based on values used in NHANES III, and estimated average daily intake during the reference year. The questionnaire also inquired about use of multivitamins which generally contain 400 IU of vitamin D. Based on this information, we estimated average daily intake of vitamin D from supplements during the reference year. Total vitamin D intake summed intake from diet and supplements.

Magnitude of association: Among Whites, dietary vitamin D was not associated with breast cancer risk (OR=1.04 for highest quartile of intake). Among African-Americans, risk significantly increased with increasing vitamin D intake (OR=1.62 for highest quartile). Elevated odds ratios were also found among Latinas (OR=1.28). Considering vitamin D from diet and supplements, slightly decreased risks were noted among Whites (OR=0.83) and Latinas (OR=0.74) for daily intake $\geq$566 IU, the highest quartile. No risk reduction was seen in African-Americans.

Prevalence: The proportion of controls with high vitamin D intake from diet (highest quartile among all controls combined) was similar among Latinas (29%) and African-Americans (27%), and considerably higher than among Whites (18%). Considering vitamin D from both diet and supplements, high intake was higher among Whites (30%) than Latinas (24%) and African-Americans (22%).

2.2.14. Phytoestrogen intake (Tables 29 and 30)

Phytoestrogens are estrogenic compounds found in plant foods or derived from plant precursors [Messina 1994, Rose 1992]. Because of their chemical structure, phytoestrogens compete with endogenous estrogens for binding with estrogen receptors, but once bound they have a far weaker estrogenic potency than endogenous estrogens and thus may act in some tissues, including the breast, as antiestrogens [Messina 1994]. In addition to this possible mechanism, phytoestrogens have been suggested to reduce cancer risk through other pathways, including effects on hormone metabolism and antioxidant effects [Messina 1994, Adlerkreutz 1991, Kurzer 1997].

Recent research has suggested that the consumption of phytoestrogen-rich foods may reduce breast cancer risk [Messina 1994, Lee 1992, Wu 1996, Ingram 1997, Zheng 1999]. However, the epidemiologic data on this relationship remains limited in scope and contains what may prove to be important inconsistencies. Most epidemiologic studies have involved Asian populations and examined the effects of traditional soy foods (e.g., tofu), protein from soy foods, or urinary excretion of phytoestrogens on breast cancer risk [Messina 1994, Lee 1992, Wu 1996, Zheng 1999, Yuan 1995, Hirose 1995, Chie 1997].Most studies have not examined menopausal status-specific effects; however, the findings that have been reported suggest that phytoestrogens may lower risk in premenopausal women but not postmenopausal women [Lee 1992, Hirose 1995]. A potentially important finding for US women was the breast cancer risk reduction associated with greater urinary excretion of phytoestrogens in Australian women age 30-84, among whom the consumption of traditional soy-based foods is low [Ingram 1997]. This recent finding suggests that the intake of phytoestrogens among non-Asian women may be sufficient to beneficially impact breast cancer risk. However, it should be noted that urine specimens in this study, while collected prior to cancer treatment, were collected post-diagnosis and therefore may not reflect the period of cancer development or preclinical progression.

To date, only one case-control study reported on the association with phytoestrogen in Hispanic women, focusing on selected foods rich in phytoestrogens [Torres-Sanchez 2000]. Among both pre- and postmenopausal women, the daily consumption of 1 or more slices of onion was associated with strong risk reductions (82% and 63%, respectively). Protective effects were also seen in premenopausal women for frequent consumption of lettuce, spinach, apples, and herbal tea.

Exposure assessment: We based the assessment of phytoestrogen intake in a nutrient database that was recently developed by Dr. Pamela Horn-Ross, a co-investigator of this study, for the assessment of phytoestrogen intake using food frequency questionnaires (FFQ). Dr. Horn-Ross conducted semistructured interviews among 118 female volunteers (58 Hispanics, 21 African-Americans, 39 Whites) to ascertain which plant-based foods were commonly consumed, where they were purchased, the brands/varieties that were purchased, and how they were prepared. Based on the responses obtained in these interviews, foods were purchased and

prepared for analysis of phytoestrogen content. A total of 127 food samples representing 112 food items/groups commonly consumed by San Francisco Bay Area women were analyzed by Dr. Stephen Barnes at the University of Alabama at Birmingham using HPLC-mass spectrometry. Seven specific phytoestrogens were measured (i.e., daidzein, genistein, formononetin, biochanin A, coumestrol, matairesinol, and secoisolariciresinol). These compounds that represent three classes of phytoestrogens found in plant foods: the isoflavones (genistein, daidzein, formononetin, and biochanin A), the coumestan (coumestrol), and the lignans (matairesinol and secoisolariciresinol).

Phytoestrogen values were then added to the nutrient database of the food frequency questionnaire used in this study. A validation/calibration study of our phytoestrogen assessment and nutrient database is currently in progress. The development of the nutrient database and sources of phytoestrogen exposure in San Francisco Bay Area women have described in more detail [Horn-Ross 2000a, Horn-Ross 2000b].

Magnitude of associations: None of the seven specific phytoestrogens, nor total phytoestrogen intake were associated with reduced breast cancer risk as hypothesized. Dr. Horn-Ross, who took the lead in this analysis, concluded that even the highest quartile of intake in non-Asian women living in the San Francisco Bay area (about 3 mg/day) is considerably lower than the average intake in Asian countries (15-30 mg/day). Thus, the findings of this study do not exclude the possibility of a protective effect of high phytoestrogen intake, as has been reported in other studies conducted in Asian populations. This study, however, did not support a previous hypothesis that dietary phytoestrogen intake may explain the lower risk of breast cancer in Hispanic women [Horn-Ross 1995]. The findings on phytoestrogen were recently published [Horn-Ross 2001, see Appendix 1].

Prevalence: High total phytoestrogen intake (highest quartile) was more common among Latinas (29%) than Whites (24%) or African-Americans (21%).

2.2.15. Summary of racial/ethnic comparison of risk and protective factors

Table 31 summarizes ethnic-specific data on the prevalence of the established and hypothesized risk factors among control women. For many of the factors considered in this study, there was a gradient in prevalence (i.e., low/intermediate/high or high/intermediate/low that parallels the incidence rates of breast cancer (i.e., lowest among Latinas, intermediate among African-Americans, highest among Whites). These factors include: education, family history of breast cancer, prior biopsy for benign breast disease, menarche, nulliparity, parity, physical activity, height, caloric intake, and alcohol consumption. These findings suggest that racial/ethnic differences in the prevalence of these factors partially explains the observed racial/ethnic differences in incidence rates. Section 2.3 presents a formal evaluation of the effect of such differences on incidence rates.

There are other factors with prevalence rates that do not parallel the incidence rates. African-American women had the highest prevalence of late natural menopause, and tall height, high BMI, and high weight gain among both pre- and post-menopausal women, and the lowest prevalence of late first full-term pregnancy and long breast-feeding.

2.2.16. Summary of racial/ethnic comparison of magnitude of associations

Tables 32 and 33 present a summary of the odds ratios by race/ethnicity for the factors considered in this analysis. Overall, the magnitude of association is similar across racial/ethnic groups for many of the exposures, though there are some notable exceptions. In contrast to our findings for Latinas and Whites and in contrast to the epidemiologic literature at large, African-Americans had no increased risks with high education (OR=0.92), positive family history of breast cancer (OR=1.10), and late natural menopause (OR=0.47), and they had no decreased risks with high parity (OR=0.90), long breast-feeding (OR=0.96 among postmenopausal women), and high waist-to-hip ratio (OR=0.98 among premenopausal women). White women had no increased risks with nulliparity (OR=0.93), late first full-term pregnancy (OR=0.60), and high caloric intake (OR=0.87), and they had no decreased risks with high parity (OR=1.06) and high total physical activity (OR=0.91 among postmenopausal women). Latina women had no increased risks with prior biopsy for benign breast disease (OR=1.11), late first full-term pregnancy (OR=1.03), and high alcohol consumption (OR=1.11), and they had no decreased risks with long breast-feeding (OR=1.13 among premenopausal women), high weight gain (OR=1.29 among premenopausal women), and time spent outdoors at age 25-30 (OR=1.27).The comparison of odds ratios across racial/ethnic groups, however, is somewhat limited by small sample size, particularly for pre- and post-menopausal women. Given the generally similar odds ratios, we used the odds ratios for all women combined in the estimation of the relative attributable risk fractions (see section 2.3)

2.3. Technical Objective 3. *Perform attributable risk calculations in order to assess to what extent racial/ethnic differences in breast cancer incidence rates are due to racial/ethnic differences in the prevalence of risk factors.*

Differences in breast cancer incidence rates between racial/ethnic groups are generally attributed to differences in the prevalence of risk factors, though few studies to date have formally assessed this issue by estimating relative attributable risk fractions for the populations being compared [Brinton 1997, Gilliland 1998].

2.3.1. Statistical methods

We applied the methods described by Lele and Whittemore [1997] to estimate relative attributable risk fractions (RAR) comparing Latinas to Whites and African-Americans to Whites. Since some of the risk factors appear to have different effects in pre- and postmenopausal women and the incidence curves are different for younger and older women, we estimated separate RAR for women aged 35-49 and women aged 50-79. The elements used for these estimations include (1) age-specific incidence rates (per 100,000) for invasive breast cancer in women aged 35-49, diagnosed in the 5-county study area between 1995 and 1998 (L: 90.7, AA: 105.25, W: 135.1); (2) age-specific incidence rates for invasive breast cancer in women aged 50-79, diagnosed in the 5-county study area between 1995 and 1998 (L: 251.2, AA: 282.3, W: 430.8); (3) race/ethnicity specific prevalence rates of exposures among controls age 35-49; (4) race/ethnicity specific prevalence rates of exposures among controls age 50-79; (5) multivariate-adjusted odds ratios for women aged 35-49 all race/ethnicities combined under the assumption that the magnitude of association does not significantly differ between racial/ethnic groups; and (6) multivariate-adjusted odds ratios for women aged 50-79 all race/ethnicities combined. Breast cancer incidence rates were obtained from the SEER registry covering the San Francisco Bay area, and race/ethnicity

specific exposure prevalence rates and overall odds ratios were derived from the case-control study. Since the RAR for individual factors are not additive, we also estimated RAR for combinations of risk factors.

2.3.2. Relative attributable risk fractions among women aged 35-49

For the exposures examined in this study, Table 34 presents odds ratios for the three racial/ethnic groups combined, exposure prevalence rates in each racial/ethnic groups, RAR comparing Latinas to Whites, and RAR comparing African-Americans to Whites.

RAR for Latinas compared to Whites: Among women aged 35-49, the incidence rate of breast cancer in 1995-1998 was 49% higher among Whites compared to Latinas. We estimated that differences in education accounted for 50% of the difference in incidence rates between the two groups. Similarly important in explaining a large proportion of the difference in incidence were height (explaining 45% of the difference), parity (37%), age at first full-term pregnancy (34%), body mass index (28%), country of birth (23%), lifetime breast-feeding (23%), central adiposity (20%), and lifetime physical activity (13%). Factors that explained very little of the difference in incidence include family history of breast cancer (3%), weight gain (2%), age at menarche (1%), and biopsy for benign breast disease (1%). Three factors produced negative RAR, including caloric intake (-10%), menopausal status (-8%), and alcohol consumption (-1%). These factors had a more favorable distribution among White women (i.e., compared to Latinas, White women had a lower caloric intake and were less likely to be premenopausal), and therefore did not explain any of the difference in incidence between White and Latina women.

For factors that individually explained 13-50% of the difference in incidence between Whites and Latinas (i.e., country of birth, education, parity, age at first full-term pregnancy, breast-feeding, height, BMI, waist-to-hip ratio and physical activity), we estimated RAR for combination of risk factors (Table 35). We recognize that RAR are very sensitive to exposure categorization, and odds ratios in turn are very sensitive to sample size in specific exposure cells. We therefore did not explore any RAR involving more than 3 factors. RAR were highest for the following combinations of risk factors: education, country of birth and parity (88%); country of birth, parity and age at first full-term pregnancy (79%); and height and waist-to-hip ratio (64%). Thus, much of the difference in incidence between Latinas and Whites aged 35-49 was explained by differences in the prevalence of established or suspected risk factors.

RAR for African-Americans compared to Whites: Among women aged 35-49, the incidence rate was 28% higher among Whites compared to African-Americans. The RAR tended to be smaller than those for Latinas compared to Whites, except for age at first full-term pregnancy, BMI, and weight gain that explained more of the difference in incidence between African-Americans and Whites than between Latinas and Whites. The RAR were largest for age at first full-term pregnancy (41%), BMI (38%), parity (24%), waist-to-hip ratio (21%), and weight gain (15%). Only a small amount of the difference in incidence were explained by education (6%) and family history of breast cancer (2%). A number of the other variables considered in this analysis did not explain the difference in incidence rates (i.e., country of birth, education, breast-feeding, height, and physical activity). Several factors had more favorable distributions among White women, and therefore produced negative RAR, including lifetime breast-feeding (-23%), height (-14%), biopsy for benign breast disease (-14%), caloric intake (-9%), menopausal status (-8%), age at menarche (-5%), alcohol consumption (-2%), and lifetime physical activity (-2%).

Combination of risk factors generally produced slightly smaller RAR for the comparison of African-Americans and Whites than for the comparison of Latinas and Whites. Unlike the high RAR for education and country of birth (71%) observed for Latinas and Whites, the RAR was small for African-Americans and Whites (3%). The most important risk factors were parity and age at first full-term pregnancy (45%, compared to 57% for Latinas and Whites); BMI and waist-to-hip ratio (43%, compared to 38% for Latinas and Whites); and height and waist-to-hip ratio (31%, compared to 64% for Latinas and Whites).

2.3.3. Relative attributable risk fractions among women aged 50-79

Relative attributable risk fractions (RAR) for women aged 50-79 comparing Latinas to Whites and African-Americans to Whites are shown in Table 36.

RAR for Latinas compared to Whites: Among women aged 50-79, the incidence rate was 72% higher among Whites compared to Latinas. Among the individual factors most important in explaining the difference in incidence are country of birth (57%), parity (34%), breast-feeding (21%), height (19%), age at first full-term pregnancy (12%), alcohol consumption (11%), family history of breast cancer (8%), and lifetime physical activity (8%). Factors that explained a small proportion of the difference in incidence include age at menarche (5%), education (3%), biopsy for benign breast disease (1%), body mass index (1%), and central adiposity (1%). Weight gain (-2%) and caloric intake (-8%) produced negative RAR.

With regard to combinations of risk factors, differences in country of birth, parity and breast-feeding accounted for 81% of the difference in incidence. High RAR were also found for parity, breast-feeding and height (44%), and for parity, breast-feeding and alcohol consumption (28%).

RAR for African-Americans compared to Whites: Among women aged 50-79, the incidence rate was 52% higher among Whites compared to African-Americans. RAR were generally lower than those noted for older Latinas and Whites (Table 36). Factors that explain some of the difference in incidence include parity (18%), age at first full-term pregnancy (12%), and alcohol consumption (9%). Parity, breast-feeding and alcohol consumption explained 51% of the difference in incidence.

2.3.4. Summary

The differences in breast cancer incidence are considerably larger among older women than among younger women, among both Whites compared to Latinas (72% and 49%) and among Whites compared to African-Americans (52% and 28%). The most striking finding of our RAR calculations is that the factors we evaluated explained less of the difference in incidence among women aged 50-79 than among women aged 35-49.

Country of birth was a powerful variable in explaining much of the difference in incidence between Latinas and Whites among both older and younger women (RAR=57% and 23%, respectively). Education was important only among younger women (RAR=50%). Both country of birth and education did not explain the difference in incidence between African-Americans and Whites. It remains to be determined what factors underlie the association with country of birth and education.

Reproductive variables were also important in partly explaining the difference in incidence, but explained more of the difference in younger women. Among women aged 35-49, parity and age at first full-term pregnancy explained about half of the difference among both Latinas/Whites (RAR=57%) and African-Americans/Whites (RAR=45%). The corresponding RAR were considerably lower among older women (RAR=23% and 9%, respectively).

A similar pattern emerged for the anthropometric measures. Combinations of height, BMI and wait-to-hip ratio explained more of the difference in younger women than older women and more of the difference between Latinas and Whites than between African-Americans and Whites.

Figure 1:
Age-specific incidence rates (per 100,000) by race/ethnicity, SEER 1992-97

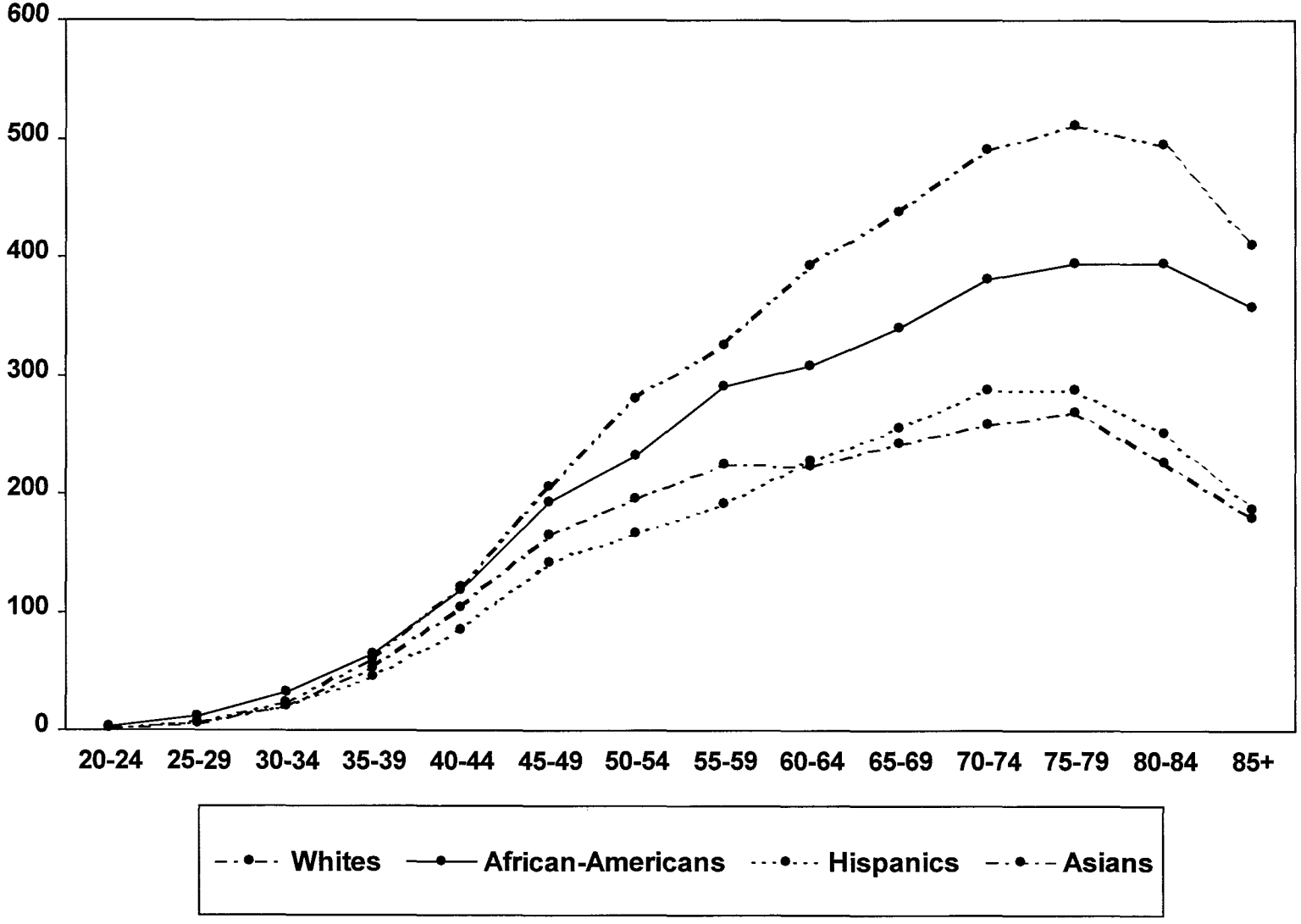


Figure 2:
Age-specific incidence rates (per 100,000) by race/ethnicity, SEER 1992-97

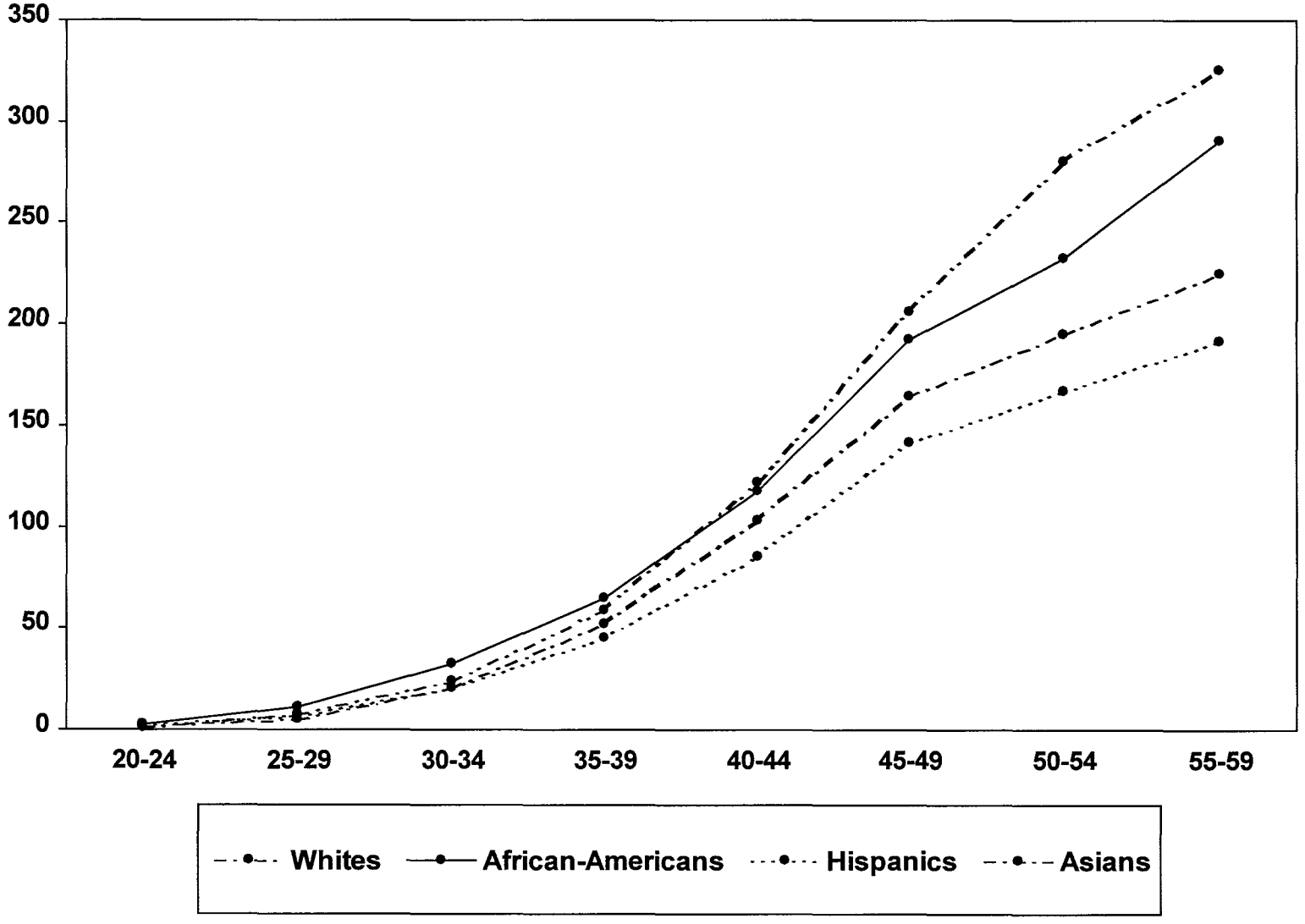


Figure 3:
Breast cancer incidence rates (per 100,000)
San Francisco Bay Area, 1973-98

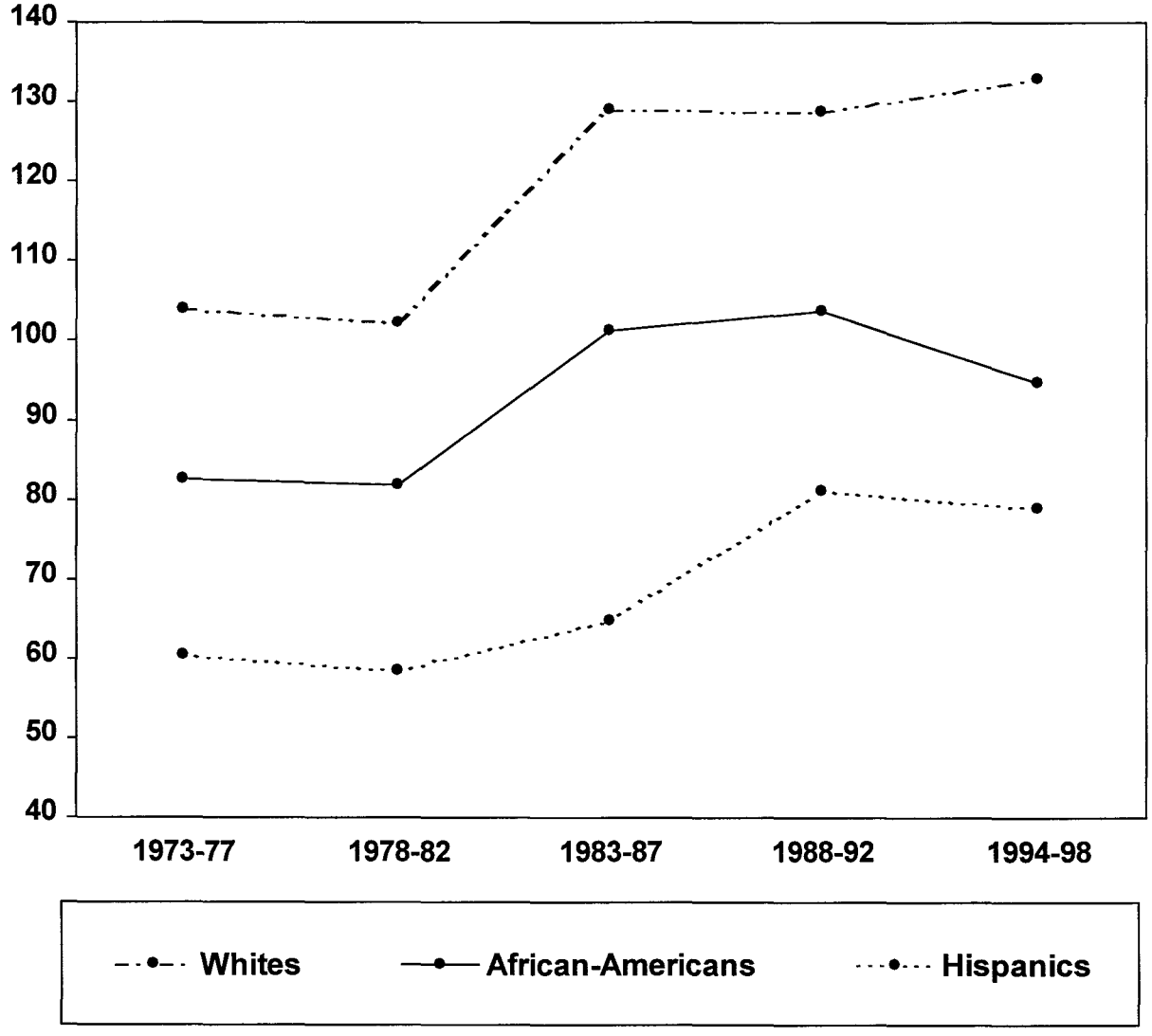


Table 1: Response rates to screening and in-person interview, by race/ethnicity The San Francisco Bay Area Breast Cancer Study

	All race/ethnicities	Hispanics	African-Americans	Whites
CASES				
Cases identified through the cancer registry	7,591			
Alive at contact	7,294			
Physician consent obtained	7,174			
Screening interview completed	6,157 (86%)			
In-person interview completed	1,326 (86%)	468 (88%)	409 (85%)	449 (86%)
CONTROLS				
Controls identified through RDD	2,389			
Alive at contact	2,376			
Screening interview completed	2,062 (87%)			
In-person interview completed	1,657 (84%)	697 (87%)	461 (82%)	499 (83%)

Table 2: Demographic and personal factors and breast cancer risk
The San Francisco Bay Area Breast Cancer Study

n=2,901	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 455	Controls 677	OR [a] 95% CI	Cases 397	Controls 449	OR [a] 95% CI	Cases 438	Controls 485	OR [a] 95% CI
Country of birth									
US born	227	214	1.0	390	437	1.0	401	441	1.0
Foreign born	228	463	0.63 0.47-0.84	7	12	0.63 0.24-1.66	37	44	1.02 0.63-1.64
Education									
<12 years	176	381	1.0	79	86	1.0	18	29	1.0
High school graduate	93	126	0.92 0.64-1.34	82	107	0.80 0.51-1.25	89	99	1.29 0.66-2.51
Some college	109	109	1.24 0.86-1.79	167	177	1.03 0.69-1.55	150	162	1.38 0.72-2.64
College graduate	77	61	1.32 0.84-2.07	69	79	0.92 0.56-1.50	181	195	1.27 0.66-2.44
Family history of breast cancer									
No	396	629	1.0	339	387	1.0	349	409	1.0
Yes	59	48	1.83 1.20-2.80	58	62	1.10 0.74-1.64	89	76	1.34 0.95-1.91
Prior biopsy for benign breast disease									
No	382	597	1.0	321	372	1.0	328	392	1.0
Yes	73	80	1.11 0.76-1.61	76	77	1.19 0.82-1.72	110	93	1.36 0.98-1.89

[a] Adjusted for age, country of birth, education, family history of breast cancer, prior biopsy for benign breast disease, age at menarche, parity, lifetime breast-feeding, lifetime physical activity, height, interaction of menopausal status and BMI.

Table 3: Prevalence of demographic and personal characteristics among controls The San Francisco Bay Area Breast Cancer Study

	CONTROLS		
	LATINAS n=677	**AFRICAN-AMERICANS** n=449	**WHITES** n=485
Country of birth			
Foreign-born	68%	3%	9%
Education			
< 12 years	56%	19%	5%
College graduate	9%	18%	40%
Family history of breast cancer			
Yes	7%	14%	16%
Prior biopsy for benign breast disease			
Yes	12%	17%	19%

Table 4: Menstrual factors and breast cancer risk
The San Francisco Bay Area Breast Cancer Study

n=1,735	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 254	Controls 421	OR [a] 95% CI	Cases 234	Controls 286	OR [a] 95% CI	Cases 254	Controls 286	OR [a] 95% CI
Age at menarche [a]									
8-11	131	142	1.0	94	96	1.0	92	98	1.0
12-13	210	310	0.81 0.59-1.11	197	229	0.86 0.60-1.23	257	267	0.93 0.66-1.32
14+	114	225	0.64 0.45-0.91	106	124	0.83 0.55-1.25	89	120	0.72 0.48-1.10
Menopausal status									
Premenopausal	395	229	1.0	123	128	1.0	113	126	1.0
Postmenopausal	276	429	0.78 0.53-1.13	268	313	0.74 0.49-1.12	299	326	0.86 0.55-1.36
Unknown	13	19	0.91 0.44-1.90	6	8	0.75 0.25-2.22	26	33	0.84 0.47-1.50
Type of menopause (postmenopausal women) [b]									
Natural	152	268	1.0	133	134	1.0	180	187	1.0
Surgical	111	144	1.36 0.99-1.87	130	168	0.78 0.56-1.09	98	127	0.80 0.57-1.12
Unknown	14	18	1.37 0.66-2.84	6	12	0.50 0.18-1.38	21	13	1.68 0.82-3.45
Age at natural menopause									
<45	25	62	1.0	29	23	1.0	11	19	1.0
45-54	97	186	1.26 0.70-2.27	79	77	0.86 0.43-1.71	135	144	1.75 0.77-3.98
55+	30	20	3.96 1.72-9.11	24	34	0.47 0.20-1.09	34	24	2.66 1.03-6.90
Age at surgical menopause [c]									
<45	85	105	1.0	97	126	1.0	58	86	1.0
45+	26	39	0.87 0.45-1.65	33	42	0.95 0.53-1.69	40	41	1.46 0.78-2.70

n=1,735	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 254	Controls 421	OR [a] 95% CI	Cases 234	Controls 286	OR [a] 95% CI	Cases 254	Controls 286	OR [a] 95% CI
Age at menopause by type									
Natural <45	25	62	1.0	29	23	1.0	11	19	1.0
Natural 45-54	97	186	1.24 0.70-2.17	79	77	0.85 0.44-1.62	135	144	1.64 0.73-3.66
Natural 55+	30	20	3.63 1.65-8.00	24	34	0.52 0.24-1.16	34	24	2.39 0.94-6.06
Surgical <45	85	105	1.59 0.88-2.86	97	126	0.58 0.31-1.09	58	86	1.11 0.48-2.55
Surgical 45+	26	39	1.32 0.63-2.75	33	42	0.55 0.27-1.15	40	41	1.56 0.65-3.78

[a] Adjusted for age, country of birth, education, family history of breast cancer, prior biopsy for benign breast disease, age at menarche, parity, lifetime breast-feeding, lifetime physical activity, height, interaction of menopausal status and BMI.

[b] Adjusted for age only.

[b] Age at surgery (i.e., hysterectomy, uni- or bilateral oophorectomy).

Table 5: Prevalence of menopausal characteristics among controls by race/ethnicity

	CONTROLS		
	LATINAS n=677	**AFRICAN-AMERICANS** n=449	**WHITES** n=485
Age at menarche			
8-11	21%	21%	20%
≥14	33%	28%	25%
Type of menopause			
Natural	62%	43%	57%
Surgical	33%	54%	39%
Unknown	4%	4%	4%
Age at natural menopause			
<45	23%	17%	10%
45-54	69%	57%	77%
≥55	7%	25%	13%
Age at surgical menopause			
<45	73%	75%	68%
≥45	27%	25%	32%

Table 6: Reproductive factors and breast cancer risk
The San Francisco Bay Area Breast Cancer Study

n=2,901	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 455	Controls 677	OR 95% CI	Cases 397	Controls 449	OR 95% CI	Cases 438	Controls 485	OR 95% CI
Parity [a]									
0	63	39	1.33 0.80-2.22	58	51	1.30 0.82-2.07	88	91	0.93 0.61-1.40
1-2	174	189	1.0	165	192	1.0	207	217	1.0
3-4	144	257	0.64 0.47-0.88	120	135	1.12 0.80-1.58	113	143	0.87 0.63-1.22
5+	74	200	0.54 0.35-0.81	54	71	0.90 0.57-1.42	30	34	1.06 0.60-1.88
Age at first-full-term pregnancy [a]									
<20	93	194	1.0	138	164	1.0	43	48	1.0
20-24	151	231	1.20 0.85-1.71	125	151	0.99 0.69-1.42	137	146	0.94 0.56-1.56
25-29	88	123	1.23 0.81-1.87	43	53	0.97 0.59-1.61	107	113	0.84 0.49-1.45
30+	60	80	1.03 0.63-1.69	32	30	1.31 0.71-2.43	63	87	0.60 0.32-1.11

[a] Adjusted for age, country of birth, education, family history of breast cancer, prior biopsy for benign breast disease, age at menarche, parity, lifetime breast-feeding, lifetime physical activity, height, and interaction of menopausal status and BMI.

[b] Adjusted for age, country of birth, education, family history of breast cancer, age at menarche, parity, lifetime breast-feeding, lifetime physical activity, and height.

Table 7: Prevalence of reproductive characteristics among controls

	CONTROLS		
	LATINAS n=677	**AFRICAN-AMERICANS** n=449	**WHITES** n=485
Nulliparity			
Nulliparous	6%	11%	19%
Parity			
≥5	30%	16%	7%
Age at first full-term pregnancy			
<20 years	29%	37%	10%
≥30	12%	7%	18%

Table 8: Breast-feeding and breast cancer risk in premenopausal parous women The San Francisco Bay Area Breast Cancer Study

n=751	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 136	Controls 217	OR [a] 95% CI	Cases 108	Controls 115	OR [a] 95% CI	Cases 80	Controls 95	OR [a] 95% CI
History of breast-feeding									
Never	35	44	1.0	56	57	1.0	22	19	1.0
Ever	101	173	1.00 0.55-1.81	52	58	0.93 0.53-1.66	58	76	0.72 0.32-1.65
Ever <2 weeks	7	13	1.18 0.37-3.8	1	4		0	5	
Ever ≥2 weeks	94	160	0.99 0.54-1.80	51	43		58	71	
Lifetime breast-feeding (months)									
0	35	44	1.0	56	57	1.0	22	19	1.0
<12	51	77	0.91 0.47-1.74	35	35	1.04 0.55-1.97	38	31	1.20 0.49-2.95
≥12	50	96	1.13 0.57-2.24	17	23	0.76 0.34-1.70	20	45	0.37 0.14-0.97
Lifetime breast-feeding without supplementation (months)									
0	36	45	1.0	57	57	1.0	24	19	1.0
<6	45	59	1.05 0.54-2.04	32	26	1.23 0.62-2.45	33	38	0.73 0.31-1.74
≥6	55	113	0.97 0.51-1.89	19	32	0.59 0.28-1.26	23	38	0.45 0.18-1.14
Average breast-feeding per child (months)									
0	35	44	1.0	56	57	1.0	22	19	1.0
<6	53	101	0.88 0.46-1.66	37	28	1.09 0.57-2.05	34	34	1.03 0.42-2.52
≥6	48	72	1.20 0.61-2.38	15	30	0.69 0.31-1.54	24	42	0.45 0.17-1.16

n=751	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 136	Controls 217	OR 95% CI	Cases 108	Controls 115	OR 95% CI	Cases 80	Controls 95	OR 95% CI
Number of children breast-fed									
0	35	44	1.0	56	57	1.0	22	19	1.0
1-2	77	111	1.00 0.55-1.84	45	47	1.00 0.55-1.81	54	63	0.82 0.35-1.90
≥3	24	62	0.96 0.40-2.28	7	11	0.60 0.18-2.10	4	13	0.26 0.05-1.36
Use of medication to stop milk production									
Never	93	175	1.0	57	55	1.0	60	77	1.0
Ever	43	42	1.62 0.89-2.92	51	60	0.81 0.45-1.44	20	18	2.19 0.91-5.24

[a] Adjusted for age, country of birth, education, family history of breast cancer, prior biopsy for benign breast disease, age at menarche, parity, age at first full-term pregnancy, and BMI.

Not adjusted for height and physical activity.

Table 9: Breast-feeding and breast cancer risk in postmenopausal parous women The San Francisco Bay Area Breast Cancer Study

n=1,735	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 254	Controls 421	OR [a] 95% CI	Cases 234	Controls 286	OR [a] 95% CI	Cases 254	Controls 286	OR [a] 95% CI
History of breast-feeding									
Never	115	128	1.0	126	147	1.0	121	130	1.0
Ever	139	293	0.76 0.53-1.09	108	139	0.85 0.58-1.23	133	156	0.89 0.62-1.28
Ever <2 weeks	7	35	0.32 0.13-0.79	7	4	2.04 0.56-7.39	8	10	0.92 0.34-2.51
Ever ≥2 weeks	132	258	0.81 0.56-1.17	100	135	0.80 0.55-1.17	125	146	0.89 0.62-1.28
Lifetime breast-feeding (months)									
0	115	128	1.0	126	147	1.0	121	130	1.0
<12	71	105	0.86 0.57-1.30	46	70	0.75 0.48-1.19	87	91	1.00 0.67-1.50
≥12	68	188	0.65 0.41-1.02	62	69	0.96 0.61-1.53	46	65	0.73 0.45-1.18
Lifetime breast-feeding without supplementation (months)									
0	116	130	1.0	129	147	1.0	122	134	1.0
<6	56	88	0.81 0.52-1.27	43	60	0.78 0.49-1.25	72	83	0.93 0.61-1.42
≥6	82	203	0.74 0.49-1.12	62	79	0.82 0.52-1.29	60	69	0.93 0.59-1.46
Average breast-feeding per child (months)									
0	115	128	1.0	126	147	1.0	121	130	1.0
<6	90	164	0.79 0.54-1.17	62	83	0.86 0.56-1.32	94	101	0.98 0.66-1.45
≥6	49	129	0.70 0.43-1.13	46	56	0.84 0.51-1.36	39	55	0.73 0.44-1.20

n=751	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 254	Controls 421	OR [a] 95% CI	Cases 234	Controls 286	OR [a] 95% CI	Cases 254	Controls 286	OR [a] 95% CI
Number of children breast-fed									
0	115	128	1.0	126	147	1.0	121	130	1.0
1-2	82	135	0.74 0.50-1.10	73	95	0.84 0.56-1.25	105	116	0.96 0.65-1.40
≥3	57	158	0.80 0.49-1.33	35	44	0.89 0.50-1.58	28	40	0.68 0.37-1.25
Use of medication to stop milk production									
Never	166	288	1.0	147	172	1.0	145	181	1.0
Ever	88	133	0.79 0.54-1.15	87	114	0.91 0.62-1.34	109	105	1.54 1.05-2.24

[a] Adjusted for age, country of birth, education, family history of breast cancer, age at menarche, age at menopause, and parity.

Not adjusted for height and physical activity.

Table 10: Prevalence of breast-feeding among controls

	CONTROLS		
	LATINAS n=677	**AFRICAN-AMERICANS** n=449	**WHITES** n=485
Lifetime breast-feeding (premenopausal women)			
None	21%	50%	21%
≥12 months	45%	19%	47%
Lifetime breast-feeding (postmenopausal women)			
None	30%	51%	46%
≥12 months	46%	24%	23%

Table 11: Exogenous hormone use and breast cancer risk
The San Francisco Bay Area Breast Cancer Study

n=2,901	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 455	Controls 677	OR [a] 95% CI	Cases 397	Controls 449	OR [a] 95% CI	Cases 438	Controls 485	OR [a] 95% CI
Use of oral contraceptives									
None	160	292	1.0	141	160	1.0	133	153	1.0
<5 yrs	148	232	1.10 0.79-1.55	92	129	0.86 0.57-1.28	125	167	0.81 0.55-1.19
5+ yrs	97	139	0.93 0.63-1.37	130	158	0.99 0.67-1.46	124	161	0.86 0.58-1.29
Use of hormone replacement therapy									
Never	291	419	1.0	266	267	1.0	164	191	1.0
<5 yrs	71	142	0.69 0.46-1.02	73	107	0.69 0.47-1.02	101	116	1.09 0.70-1.68
5+ yrs	84	105	0.87 0.59-1.29	55	70	0.79 0.51-1.22	166	172	1.11 0.74-1.65
Use of hormone replacement therapy									
Never	291	419	1.0	266	267	1.0	164	191	1.0
Past user	66	85	1.09 0.73-1.65	60	70	0.87 0.57-1.33	90	61	1.74 1.11-2.73
Current user	93	162	0.65 0.45-0.94	68	108	0.62 0.41-0.93	178	228	0.87 0.59-1.30

[a] Adjusted for age, country of birth, education, family history of breast cancer, prior biopsy for benign breast disease, age at menarche, parity, lifetime breast-feeding, lifetime physical activity, height, interaction of menopausal status and BMI.

Table 12: Prevalence of exogenous hormone use among controls by race/ethnicity

	CONTROLS		
	LATINAS n=677	**AFRICAN-AMERICANS** n=449	**WHITES** n=485
Use of oral contraceptives			
Yes	56%	64%	68%
≥5 years	21%	35%	33%
Use of hormone replacement therapy			
Yes	37%	40%	60%
≥5 years	16%	16%	36%
Current use	24%	24%	48%

Table 13: Body size characteristics and breast cancer risk in premenopausal women The San Francisco Bay Area Breast Cancer Study

n=884	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 166	Controls 228	OR [a] 95% CI	Cases 123	Controls 128	OR [a] 95% CI	Cases 113	Controls 126	OR [a] 95% CI
Height (cm)									
<157	67	119	1.0	14	19	1.0	10	21	1.0
157-163	66	77	1.32 0.80-2.17	39	41	1.44 0.59-3.54	34	45	1.80 0.70-4.68
≥164	33	32	1.18 0.62-2.27	70	68	1.39 0.61-3.18	69	60	2.83 1.14-7.05
BMI									
≤25	51	40	1.0	26	26	1.0	61	60	1.0
25.1-30.0	55	89	0.48 0.26-0.86	37	35	1.00 0.45-2.18	25	31	0.87 0.42-1.80
≥30.1	60	99	0.53 0.29-0.99	60	67	0.80 0.39-1.67	27	35	0.67 0.33-1.38
Waist-to-hip ratio									
<0.77	59	51	1.0	32	30	1.0	71	70	1.0
0.77-0.82	49	85	0.59 0.32-1.08	28	33	0.76 0.33-1.76	23	32	0.68 0.32-1.44
≥0.83	51	84	0.69 0.36-1.34	48	50	0.98 0.44-2.20	10	17	0.53 0.19-1.52
Weight gain since age 25 (kg)									
<9.3	53	58	1.0	22	20	1.0	45	50	1.0
9.3-20.6	51	89	0.82 0.43-1.56	42	33	1.17 0.49-2.80	31	36	0.73 0.29-1.84
≥20.7	48	60	1.29 0.55-3.03	54	64	0.60 0.21-1.73	21	32	0.39 0.10-1.45

[a] Adjusted for age, country of birth, education, family history of breast cancer, prior biopsy for benign breast disease, age at menarche, parity, age at first full-term pregnancy, lifetime breast-feeding, and physical activity.

Table 14: Body size characteristics and breast cancer risk in postmenopausal women The San Francisco Bay Area Breast Cancer Study

n=1,912	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 278	Controls 421	OR [a] 95% CI	Cases 270	Controls 316	OR [a] 95% CI	Cases 299	Controls 328	OR [a] 95% CI
Height (cm)									
<156	138	244	1.0	32	42	1.0	50	70	1.0
156-162	96	127	1.15 0.80-1.65	89	113	1.10 0.63-1.92	116	107	1.54 0.97-2.46
≥163	43	50	1.41 0.85-2.34	147	159	1.39 0.81-2.39	133	150	1.27 0.80-2.01
BMI									
≤25	54	65	1.0	43	58	1.0	123	122	1.0
25.1-30.0	105	170	1.01 0.63-1.60	81	93	1.31 0.79-2.19	89	106	0.89 0.60-1.32
≥30.1	118	185	0.97 0.61-1.54	144	162	1.33 0.83-2.14	87	98	0.98 0.64-1.49
BMI - no HRT									
≤25	24	23	1.0	23	23	1.0	14	31	1.0
25.1-30.0	48	75	1.22 0.57-2.59	45	41	1.44 0.67-3.11	17	20	2.39 0.82-7.0
≥30.1	62	92	1.27 0.60-2.70	81	80	1.32 0.65-2.71	29	24	3.43 1.23-9.5
BMI - HRT use									
≤25	30	42	1.0	19	35	1.0	109	89	1.0
25.1-30.0	55	93	0.92 0.50-1.71	36	50	1.36 0.65-2.86	70	84	0.71 0.45-1.10
≥30.1	55	90	0.81 0.43-1.52	62	81	1.33 0.67-2.65	57	74	0.68 0.42-1.13
Waist-to-hip ratio									
<0.80	78	116	1.0	54	60	1.0	131	137	1.0
0.80-0.85	88	144	1.02 0.67-1.55	73	84	0.94 0.57-1.55	83	85	1.13 0.75-1.71
≥0.86	94	140	1.28 0.83-1.99	92	110	0.91 0.56-1.49	52	64	0.90 0.55-1.46

n=1,912	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 278	Controls 421	OR [a] 95% CI	Cases 270	Controls 316	OR [a] 95% CI	Cases 299	Controls 328	OR [a] 95% CI
Weight gain since age 25 (kg)									
<10	57	98	1.0	40	47	1.0	96	100	1.0
10-21.5	97	143	1.29 0.86-1.93	77	90	1.06 0.66-1.70	103	105	1.20 0.82-1.77
≥21.5	73	100	1.27 0.82-1.99	129	153	1.05 0.68-1.63	75	86	1.13 0.74-1.73

[a] Adjusted for age, country of birth, education, family history of breast cancer, age at menarche, age at menopause, parity.

Table 15: Prevalence of body size characteristics among controls, by race/ethnicity

	CONTROLS		
	LATINAS	**AFRICAN-AMERICANS**	**WHITES**
PREMENOPAUSAL WOMEN	**n=228**	**n=128**	**n=126**
Height (cm)			
<157	52%	15%	17%
≥164	14%	53%	48%
BMI			
≤25	18%	20%	48%
≥30.1	43%	52%	28%
Waist-to-hip ratio			
<0.77	23%	27%	59%
≥0.83	38%	44%	14%
Weight gain since age 25 (kg)			
<9.3	28%	17%	42%
≥20.7	29%	55%	27%
POSTMENOPAUSAL WOMEN	**n=421**	**n=316**	**n=328**
Height (cm)			
<156	58%	13%	21%
≥163	12%	51%	46%
BMI			
≤25	15%	19%	37%
≥30.1	44%	52%	30%
Waist-to-hip ratio			
<0.80	29%	24%	48%
≥0.86	35%	43%	22%
Weight gain since age 25 (kg)			
<10.0	29%	16%	34%
≥21.5	29%	53%	30%

Table 16: Dietary factors and alcohol consumption and breast cancer risk
The San Francisco Bay Area Breast Cancer Study

n=2,805	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 439	Controls 656	OR [a] 95% CI	Cases 368	Controls 434	OR [a] 95% CI	Cases 430	Controls 478	OR [a] 95% CI
Caloric intake (kcal/day)									
<1608	105	153	1.0	129	185	1.0	179	184	1.0
1608-2365	156	211	1.25 0.88-1.77	124	121	1.49 1.05-2.12	168	190	0.93 0.68-1.26
≥2366	178	292	1.23 0.87-1.74	115	128	1.37 0.95-1.98	83	104	0.87 0.60-1.28
Fat intake (g/day)									
<50	120	193	1.0	100	161	1.0	156	168	1.0
50-79	156	231	1.11 0.80-1.55	113	113	1.69 1.16-2.47	166	178	1.07 0.78-1.48
≥80	163	232	1.21 0.86-1.69	155	160	1.60 1.12-2.28	108	132	0.97 0.68-1.39
Alcohol consumption (g/day)									
0	174	304	1.0	170	187	1.0	90	110	1.0
0.1-4.9	192	275	0.89 0.66-1.20	130	170	0.81 0.58-1.13	176	218	0.89 0.62-1.27
5.0-9.9	31	40	0.77 0.44-1.35	20	34	0.65 0.35-1.19	51	56	0.96 0.58-1.58
≥10	41	36	1.11 0.65-1.90	48	42	1.22 0.74-1.99	112	93	1.30 0.86-1.98

[a] Analysis excluded 96individuals with total caloric intake per day of <600 or >5000.

[a] Adjusted for age, country of birth, education, family history of breast cancer, prior biopsy for benign breast disease, age at menarche, parity, lifetime breast-feeding, lifetime physical activity, height, interaction of menopausal status and BMI.

Table 17: Prevalence of dietary factors and alcohol consumption among controls, by race/ethnicity

	CONTROLS		
	LATINAS n=677	**AFRICAN-AMERICANS** n=449	**WHITES** n=485
Caloric intake (kcal/day)			
<1608	23%	43%	38%
≥2366	45%	29%	22%
Fat intake (g/day)			
<50	29%	37%	35%
≥80	35%	37%	28%
Alcohol consumption (g/day)			
0	46%	43%	23%
≥10	5%	10%	19%

Table 18: Physical activity and breast cancer risk in premenopausal women The San Francisco Bay Area Breast Cancer Study

n=884	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 166	Controls 228	OR [a] 95% CI	Cases 123	Controls 128	OR [a] 95% CI	Cases 113	Controls 126	OR [a] 95% CI
EXERCISE AND SPORTS									
Exercise (hrs/wk)									
<1.5	100	141	1.0	54	63	1.0	46	46	1.0
1.5-3.9	34	48	0.77 0.43-1.38	29	28	1.20 0.61-2.39	34	42	0.81 0.41-1.60
≥4.0	32	39	0.76 0.41-1.42	41	37	1.37 0.73-2.55	33	39	0.79 0.39-1.60
Exercise (Met-hrs)									
<6	92	140	1.0	48	55	1.0	34	40	1.0
6-17	37	46	1.03 0.58-1.82	31	32	1.04 0.53-2.05	40	42	1.13 0.56-2.28
≥18	37	42	0.87 0.47-1.89	45	41	1.36 0.73-2.54	39	45	0.92 0.45-1.87
Years exercising ≥4+ hrs/wk									
0	77	121	1.0	42	55	1.0	27	30	1.0
1-11	54	61	1.59 0.67-3.75	34	29	1.04 0.40-2.65	48	52	1.19 0.49-2.91
≥12	35	46	0.66 0.22-2.00	48	44	1.57 0.50-4.94	38	45	0.81 0.27-2.42
WALKING AND BICYCLING									
Walk/bike (hrs/wk)									
<0.2	64	72	1.0	49	47	1.0	45	41	1.0
0.2-0.5	53	65	0.63 0.36-1.13	39	49	0.76 0.41-1.42	42	48	0.77 0.40-1.50
≥0.6	49	91	0.57 0.33-0.99	36	32	1.12 0.56-2.23	26	38	0.59 0.28-1.24
STRENUOUS CHORES (INDOOR AND OUTDOOR)									
Chores (hrs/wk)									
<3.4	58	61	1.0	52	42	1.0	59	58	1.0
3.4-8.4	57	65	0.96 0.55-1.67	53	59	0.68 0.38-1.23	33	37	1.00 0.50-2.00
≥8.5	51	102	0.74 0.42-1.31	19	27	0.57 0.26-1.25	21	32	0.76 0.33-1.74

n=884	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 166	Controls 228	OR [a] 95% CI	Cases 123	Controls 128	OR [a] 95% CI	Cases 113	Controls 126	OR [a] 95% CI
NON-OCCUPATIONAL ACTIVITY (EXERCISE, WALKING, BICYCLING, STRENUOUS CHORES)									
Activity (hrs/wk)									
<6.2	55	67	1.0	40	49	1.0	49	45	1.0
6.2-13.6	71	70	1.33 0.78-2.26	53	44	1.62 0.88-3.00	46	47	1.06 0.56-1.99
≥13.7	40	91	0.70 0.39-1.24	31	35	1.09 0.55-2.17	18	35	0.41 0.18-0.96
OCCUPATIONAL ACTIVITY									
Moderate or strenuous jobs (hrs/wk)									
0	90	112	1.0	79	72	1.0	68	66	1.0
<10.0	43	57	1.07 0.62-1.84	21	24	0.88 0.43-1.81	26	36	0.93 0.46-1.85
≥10.0	33	59	0.87 0.49-1.55	24	32	0.67 0.35-1.28	19	25	0.87 0.40-1.91
TOTAL PHYSICAL ACTIVITY (NON-OCCUPATIONAL AND OCCUPATIONAL)									
Total activity (hrs/wk)									
<9.1	66	63	1.0	50	47	1.0	54	51	1.0
9.1-20.7	52	75	0.84 0.49-1.45	45	44	1.00 0.55-1.84	36	41	0.82 0.42-1.58
≥20.8	48	90	0.73 0.42-1.28	29	37	0.68 0.35-1.34	23	35	0.76 0.36-1.61
Total activity (MET-hrs)									
<45	65	65	1.0	49	48	1.0	57	48	1.0
45-99	48	72	0.85 0.49-1.49	47	43	1.14 0.62-2.09	29	45	0.54 0.28-1.05
≥100	53	91	0.82 0.47-1.41	28	37	0.70 0.36-1.37	27	34	0.81 0.38-1.67

[a] Adjusted for age, country of birth, education, family history of breast cancer, prior biopsy for benign breast disease, age at menarche, parity, age at first full-term pregnancy, lifetime breast-feeding, BMI, and other components of physical activity.

Not adjusted for height

Table 19: Mean hours per week of lifetime physical activity by type of activity among premenopausal controls
The San Francisco Bay Area Breast Cancer Study

	Latinas n=228		African-Americans n=128		Whites n=126	
Total physical activity	19.9	100%	16.9	100%	16.4	100%
Exercise and sports	1.9	10%	3.3	19%	3.5	21%
Walking/biking to school or work	0.8	4%	0.6	4%	0.5	3%
Strenuous household chores	8.8	44%	6.3	37%	5.9	36%
Strenuous outdoor chores	2.0	10%	0.5	3%	1.4	9%
Mostly moderate or strenuous jobs	6.3	32%	6.2	37%	5.1	31%

Table 20: Leading sports and exercise activities reported by premenopausal controls
The San Francisco Bay Area Breast Cancer Study

	Latinas n=228	African-Americans n=128	Whites n=126
Walking	12.1%	10.9%	7.5%
Jogging	9.8%	8.0%	8.3%
Bicycling	9.8%		10.8%
Dancing	9.0%	10.2%	
Aerobics	7.7%	10.7%	8.5%
Exercise equipment		7.5%	
Swimming			6.1%

Table 21: Prevalence of physical activity among controls

	CONTROLS		
	LATINAS	**AFRICAN-AMERICANS**	**WHITES**
PREMENOPAUSAL WOMEN	**n=228**	**n=128**	**n=126**
Lifetime exercise (hrs/wk)			
< 0.5	48%	31%	16%
≥4	17%	29%	31%
Lifetime total physical activity (hrs/wk)			
<9.2	28%	37%	40%
≥20.8	39%	29%	27%
POSTMENOPAUSAL WOMEN	**n=421**	**n=316**	**n=328**
Lifetime exercise (hrs/wk)			
< 0.5	52%	36%	23%
≥4	13%	20%	23%
Lifetime total physical activity (hrs/wk)			
<9.6	28%	35%	40%
≥21.7	42%	33%	24%

Table 22: Physical activity and breast cancer risk in postmenopausal women The San Francisco Bay Area Breast Cancer Study

n=1,912	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 278	Controls 421	OR [a] 95% CI	Cases 270	Controls 316	OR [a] 95% CI	Cases 299	Controls 328	OR [a] 95% CI
EXERCISE AND SPORTS									
Exercise (hrs/wk)									
<1.5	169	290	1.0	154	181	1.0	141	164	1.0
1.5-3.9	64	78	1.23 0.82-1.85	55	72	0.97 0.63-1.48	81	89	1.06 0.72-1.57
≥4.0	45	53	1.30 0.81-2.08	61	63	1.25 0.81-1.93	77	75	1.37 0.91-2.06
Exercise (Met-hrs)									
<6	160	281	1.0	149	174	1.0	132	155	1.0
6-17	73	85	1.24 0.83-1.85	61	76	1.02 0.66-1.55	87	94	1.11 0.75-1.64
≥18	45	55	1.22 0.76-1.95	60	66	1.17 0.76-1.82	80	79	1.37 0.91-2.07
Years exercising ≥4 hrs/wk									
0	130	235	1.0	124	139	1.0	98	103	1.0
1-11	72	94	0.67 0.37-1.22	61	77	1.13 0.61-2.08	79	101	0.63 0.38-1.04
≥12	76	92	2.07 1.05-4.06	85	100	0.74 0.3/-1.46	122	124	1.49 0.84-2.64
WALKING AND BICYCLING									
Walk/bike (hrs/wk)									
<0.2	107	150	1.0	80	102	1.0	88	103	1.0
0.2-0.5	71	118	0.64 0.42-0.98	95	110	1.12 0.73-1.71	122	125	1.13 0.76-1.67
≥0.6	100	153	0.85 0.57-1.26	95	104	1.18 0.77-1.81	89	100	1.11 0.72-1.71
STRENUOUS CHORES (INDOOR AND OUTDOOR)									
Chores (hrs/wk)									
<3.4	85	125	1.0	125	130	1.0	108	99	1.0
3.4-8.4	80	93	1.25 0.81-1.95	87	119	0.77 0.52-1.12	99	141	0.68 0.46-1.02
≥8.5	113	200	1.08 0.72-1.62	58	67	0.93 0.59-1.46	92	88	1.03 0.66-1.61

n=1,912	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 166	Controls 228	OR [a] 95% CI	Cases 123	Controls 128	OR [a] 95% CI	Cases 113	Controls 126	OR [a] 95% CI
NON-OCCUPATIONAL ACTIVITY (EXERCISE, WALKING, BICYCLING, STRENUOUS CHORES)									
Activity (hrs/wk)									
<6.2	83	124	1.0	116	125	1.0	111	106	1.0
6.2-13.6	88	113	1.18 0.77-1.80	94	117	0.88 0.60-1.29	93	124	0.73 0.49-1.08
13.7+	107	184	1.12 0.75-1.68	60	74	0.90 0.58-1.39	95	98	0.98 0.65-1.48
OCCUPATIONAL ACTIVITY									
Moderate or strenuous jobs (hrs/wk)									
0	146	195	1.0	129	143	1.0	196	175	1.0
<10.0	65	100	0.88 0.59-1.32	71	78	1.01 0.66-1.52	64	98	0.65 0.44-0.96
≥10.0	67	126	0.68 0.46-1.01	70	95	0.77 0.51-1.16	39	55	0.62 0.39-1.00
TOTAL PHYSICAL ACTIVITY (NON-OCCUPATIONAL AND OCCUPATIONAL)									
Total activity (hrs/wk)									
<9.1	95	114	1.0	111	110	1.0	129	130	1.0
9.1-20.7	84	133	0.82 0.55-1.24	82	103	0.78 0.52-1.17	101	119	0.94 0.641.37
≥20.8	99	174	0.81 0.54-1.22	77	103	0.71 0.47-1.07	69	79	0.91 0.60-1.41
Total activity (MET-hrs)									
<45	94	113	1.0	110	113	1.0	128	128	1.0
45-99	87	132	0.85 0.56-1.28	85	101	0.84 0.56-1.25	96	122	0.89 0.61-1.31
≥100	97	176	0.77 0.51-1.15	75	102	0.72 0.48-1.09	75	78	0.98 0.64-1.50

[a] Adjusted for age, country of birth, education, family history of breast cancer, age at menarche, age at menopause, parity, lifetime breast-feeding, and other components of physical activity.

Not adjusted for height

Table 23: Mean hours per week of lifetime physical activity by type of activity among postmenopausal controls
The San Francisco Bay Area Breast Cancer Study

	Latinas n=421		African-Americans n=316		Whites n=328	
Total physical activity	21.7	100%	18.1	100%	15.6	100%
Exercise and sports	1.7	8%	2.3	13%	2.7	17%
Walking/bicycling to school or work	0.7	3%	0.6	3%	0.4	3%
Strenuous household chores	10.5	48%	6.5	36%	6.9	44%
Strenuous outdoor chores	1.9	9%	1.0	5%	1.4	9%
Moderate or strenuous jobs	6.9	32%	7.8	43%	4.3	27%

Table 24: Leading sports and exercise activities reported by postmenopausal controls
The San Francisco Bay Area Breast Cancer Study

	Latinas n=421	African-Americans n=316	Whites n=328
Walking	17.0%	15%	13%
Dancing	10.8%	13%	6.9%
Bicycling	8.7%		10.0%
Jogging	7.6%	7.3%	
Speed walking	7.6%		
Exercise equipment		7.9%	
Bowling		7.3%	
Swimming			6.8%
Aerobics			6.7%

Table 25: Sunlight exposure and breast cancer risk
The San Francisco Bay Area Breast Cancer Study

n=2,901	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 455	Controls 677	OR [a] 95% CI	Cases 397	Controls 449	OR [a] 95% CI	Cases 438	Controls 485	OR [a] 95% CI
Time outdoors at age 10-15 (hrs/wk)									
< 2	103	201	1.0	57	53	1.0	68	70	1.0
3-4	156	191	1.49 1.06-2.09	121	139	0.83 0.52-1.31	137	156	0.87 0.57-1.33
5-6	96	138	1.28 0.87-1.87	114	137	0.80 0.51-1.27	144	146	0.99 0.65-1.51
≥7	96	144	1.35 0.92-1.98	102	118	0.89 0.52-1.34	89	110	0.87 0.55-1.38
Time outdoors at age 25-30 (hrs/wk)									
< 1	55	83	1.0	58	39	1.0	50	43	1.0
1-2	176	244	1.05 0.69-1.61	127	181	0.40 0.24-0.65	195	215	0.82 0.51-1.31
3-4	118	178	1.00 0.64-1.55	123	147	0.50 0.31-0.83	141	161	0.81 0.50-1.31
5-6	60	96	1.08 0.65-1.79	59	49	0.76 0.42-1.37	33	38	0.71 0.37-1.36
≥7	45	74	1.27 0.73-2.20	29	33	0.55 0.28-1.08	18	27	0.65 0.30-1.39
Time outdoors at age 50-55 (hrs/wk) (women ≥55 only)									
< 1	43	69	1.0	58	40	1.0	55	38	1.0
1-2	83	138	0.98 0.59-1.63	75	114	0.45 0.27-0.76	120	138	0.61 0.37-1.01
3-4	53	66	1.35 0.76-2.38	59	52	0.83 0.47-1.49	62	69	0.61 0.35-1.06
≥5	35	47	1.57 0.84-2.96	24	30	0.56 0.28-1.13	24	18	0.87 0.41-1.86
Lifetime average time outdoors (hrs/wk)									
<1	121	187	1.0	123	118	1.0	103	106	1.0
1-2.9	150	229	1.12 0.80-1.58	146	180	0.79 0.56-1.13	159	169	0.98 0.68-1.40
≥3	184	261	1.56 1.10-2.20	128	151	0.89 0.60-1.31	176	210	0.94 0.64-1.37

n=2,901	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 455	Controls 677	OR [a] 95% CI	Cases 397	Controls 449	OR [a] 95% CI	Cases 438	Controls 485	OR [a] 95% CI
Measured sunlight exposure [b]									
1 (low)	58	55	1.0	107	140	1.0	26	44	1.0
2	82	120	0.88 0.55-1.44	105	104	1.29 0.90-1.86	78	74	1.15 0.65-2.03
3	101	145	0.84 0.52-1.35	55	64	1.15 0.73-1.82	99	108	1.04 0.59-1.82
4	105	167	0.93 0.57-1.52	39	39	1.24 0.71-2.18	100	113	1.00 0.56-1.79
5 (high)	98	166	0.85 0.50-1.43	25	34	0.88 0.44-1.76	109	134	1.04 0.57-1.90
Average lifetime residential geographic latitude [c]									
High	76	229	1.0	129	153	1.0	108	141	1.0
Medium	137	229	0.65 0.39-1.07	130	132	1.21 0.84-1.72	179	188	0.96 0.70-1.33
Low	246	230	0.41 0.23-0.72	140	172	1.01 0.70-1.44	159	165	0.79 0.56-1.12

[a] Adjusted for age, country of birth, education, family history of breast cancer, prior biopsy for benign breast disease, age at menarche, parity, lifetime breast-feeding, lifetime physical activity, height, interaction of menopausal status and BMI.

[b] Also adjusted for constitutive skin pigmentation.

[c] L: ≥34.0, 25.3-33.9, <25.3
AA: ≥37.0, 35.6-36.9, <35.6
W: ≥38.2, 37.0-38.1, <37.0

Table 26: Constitutional and behavioral factors related to vitamin D synthesis and breast cancer risk The San Francisco Bay Area Breast Cancer Study

n=2,901	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 455	Controls 677	OR [a] 95% CI	Cases 397	Controls 449	OR [a] 95% CI	Cases 438	Controls 485	OR [a] 95% CI
CONSTITUTIONAL FACTORS									
Constitutive skin pigmentation [b]									
Dark	148	223	1.0	150	143	1.0	160	159	1.0
Medium	161	222	1.01 0.74-1.38	103	144	0.68 0.47-0.96	151	159	0.91 0.66-1.26
Light	142	224	0.81 0.59-1.12	122	144	0.81 0.57-1.15	117	160	0.70 0.50-0.98
Skin reaction to one *hour exposure to hot* sun									
Severe burn/blisters	42	70	1.0	20	14	1.0	62	99	1.0
Moderate burn	135	202	1.13 0.71-1.80	36	52	0.56 0.24-1.29	143	150	1.48 0.98-2.22
Mild burn	179	274	1.01 0.64-1.59	166	156	0.79 0.38-1.66	171	179	1.54 1.04-2.29
No burn	82	118	0.94 0.56-1.57	157	210	0.55 0.26-1.16	56	54	1.74 1.05-2.88
Tanning									
No tan	31	69	1.0	43	38	1.0	48	62	1.0
Light tan	85	154	1.33 0.79-2.26	102	98	0.86 0.50-1.47	98	113	1.27 0.78-2.06
Moderate tan	124	188	1.35 0.81-2.25	119	133	0.77 0.46-1.29	176	168	1.45 0.92-2.27
Deep tan	196	232	1.56 0.95-2.56	119	167	0.61 0.36-1.02	107	120	1.24 0.77-2.01

n=2,901	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 455	Controls 677	OR [a] 95% CI	Cases 397	Controls 449	OR [a] 95% CI	Cases 438	Controls 485	OR [a] 95% CI
BEHAVIORAL FACTORS									
Protection from sun exposure [c]									
Yes	295	218	1.0	252	284	1.0	245	269	1.0
No	158	458	1.04 0.79-1.37	145	165	0.98 0.73-1.32	193	216	0.97 0.74-1.27
Use of sunscreen									
≥Half the time	86	129	1.0	39	58	1.0	179	223	1.0
Sometimes	118	151	1.19 0.80-1.76	71	83	1.15 0.67-1.96	151	162	1.14 0.84-1.55
Never	251	396	1.40 0.98-2.01	287	308	1.37 0.86-2.18	107	100	1.47 1.03-2.12

[a] Adjusted for age, country of birth, education, family history of breast cancer, prior biopsy for benign breast disease, age at menarche, parity, lifetime breast-feeding, lifetime physical activity, height, interaction of menopausal status and BMI.

[b] Natural skin color measured at the upper inner arm (non sun-exposed site).

Cut-points for the 3 exposure categories were selected according to the race/ethnic-specific tertile distributions among controls.

[c] Any of four protective measures used most of the time when outdoors (i.e., staying in the shade, wearing of a big hat, long sleeves or long pants).

Table 27: Dietary vitamin D and breast cancer risk
The San Francisco Bay Area Breast Cancer Study

n=2,901	LATINAS			AFRICAN-AMERICANS			WHITES		
	Cases 455	Controls 677	OR [a] 95% CI	Cases 397	Controls 449	OR [a] 95% CI	Cases 438	Controls 485	OR [a] 95% CI
Vitamin D from diet only (IU/day)									
<126	97	146	1.0	78	124	1.0	116	127	1.0
126-197	104	171	1.09 0.74-1.61	78	92	1.44 0.94-2.20	126	133	1.05 0.73-1.52
198-304	126	159	1.39 0.95-2.04	100	105	1.56 1.03-2.34	111	135	0.90 0.62-1.31
≥305	118	190	1.28 0.88-1.88	115	118	1.62 1.09-2.40	87	92	1.04 0.69-1.57
Vitamin D from diet and supplements (IU/day)									
<164	124	179	1.0	92	107	1.0	103	111	1.0
164-319	126	179	1.08 0.76-1.54	94	114	0.94 0.63-1.41	114	105	1.23 0.83-1.83
320-565	109	148	1.18 0.82-1.70	93	120	0.93 0.62-1.39	112	127	0.90 0.61-1.32
≥566	86	160	0.74 0.54-1.08	92	98	1.12 0.74-1.69	111	144	0.83 0.56-1.22

a Adjusted for age, country of birth, education, family history of breast cancer, prior biopsy for benign breast disease, age at menarche, parity, lifetime breast-feeding, lifetime physical activity, height, interaction of menopausal status and BMI.

b Natural skin color measured at the upper inner arm (non sun-exposed site).

c Any of four protective measures used most of the time when outdoors (i.e., staying in the shade, wearing of a big hat, long sleeves or long pants).

Table 28: Prevalence of sun exposure and dietary vitamin D among controls

	CONTROLS		
	LATINAS n=677	**AFRICAN-AMERICANS** n=449	**WHITES** n=485
Lifetime average time spent outdoors (hrs/week)			
<1	28%	26%	22%
≥3	39%	34%	43%
Measured sun exposure			
Low	8%	37%	9%
High	25%	9%	28%
Vitamin D from diet and supplements (IU/day)			
<126	27%	24%	23%
≥305	24%	22%	30%

Table 29: Phytoestrogen intake and breast cancer risk
The San Francisco Bay Area Breast Cancer Study

n=2,882	LATINAS				AFRICAN-AMERICANS				WHITES			
	Cases n=453	Controls n=675	OR [a]	95% CI	Cases n=379	Controls n=444	OR [a]	95% CI	Cases n=440	Controls n=491	OR [a]	95% CI
ISOFLAVONES (μg/day)												
Biochanin A												
<21.5	82	128	1.00		102	142	1.00		113	132	1.00	
21.5 - 42.3	96	149	1.15	0.76-1.73	113	115	1.37	0.93-2.03	114	139	0.99	0.69-1.43
42.4 - 81.8	126	158	1.40	0.93-2.11	81	126	0.92	0.60-1.40	111	118	1.14	0.78-1.68
≥81.9	149	240	1.10	0.74-1.63	83	61	1.91*	1.18-3.08	102	102	1.24	0.82-1.87
Mean	91.1	101.3			57.5	53.2			76.3	68.9		
Genistein												
<479.9	102	163	1.00		112	141	1.00		90	98	1.00	
479.9 -783.7	105	158	0.93	0.64-1.37	83	102	1.03	0.68-1.54	133	143	1.02	0.69-1.51
783.8 - 1438.8	126	169	1.09	0.75-1.59	107	100	1.29	0.86-1.95	126	133	1.12	0.74-1.68
≥1438.9	120	185	1.00	0.67-1.49	77	101	0.92	0.58-1.46	91	117	0.84	0.54-1.30
Mean	1416.7	1483.6			1389.4	1446.1			1415.2	1582.1		
Daidzein												
<472.9	92	172	1.00		118	152	1.00		78	78	1.00	
472.9 - 747.1	120	159	1.22	0.84-1.78	95	100	1.23	0.83-1.81	129	144	0.92	0.61-1.38
747.2 - 1222.2	109	169	1.09	0.74-1.62	87	94	1.14	0.74-1.73	127	139	0.94	0.61-1.44
≥1222.3	132	175	1.43	0.95-2.14	79	98	0.96	0.61-1.53	106	130	0.81	0.52-1.26
Mean	1235.7	1249.8			1201.7	1232.8			1281.7	1448.2		

n=2,901	LATINAS				AFRICAN-AMERICANS				WHITES			
	Cases n=453	Controls n=675	OR [a]	95% CI	Cases n=379	Controls n=444	OR [a]	95% CI	Cases n=440	Controls n=491	OR [a]	95% CI
Formononetin												
<8.7	86	167	1.00		96	127	1.00		83	108	1.00	
8.7 - 19.6	102	170	1.14	0.77-1.67	100	101	1.48	0.98-2.22	116	132	1.19	0.80-1.77
19.7 - 39.5	137	155	1.67*	1.14-2.45	90	107	1.08	0.71-1.65	136	140	1.32	0.89-1.95
≥39.6	128	183	1.49*	1.00-2.21	103	109	1.31	0.85-2.01	105	111	1.29	0.84-1.96
Mean	38.2	36.7			34.0	34.1			37.9	34.0		
Total Isoflavones												
<1048.0	91	162	1.00		117	154	1.00		84	86	1.00	
1048.0 - 1648.3	113	157	1.11	0.75-1.64	86	95	1.20	0.80-1.80	133	151	0.89	0.60-1.32
1648.4 - 2773.6	124	167	1.18	0.80-1.75	99	101	1.25	0.83-1.89	126	134	1.01	0.67-1.55
≥2773.7	125	189	1.17	0.78-1.76	77	94	1.04	0.65-1.67	97	120	0.82	0.52-1.28
Mean	2781.8	2871.4			2682.6	2766.2			2811.1	3133.2		
COUMESTAN (μg/day)												
Coumestrol												
<119.3	86	139	1.00		100	151	1.00		99	112	1.00	
119.3 - 183.3	90	146	0.92	0.61-1.38	106	99	1.78*	1.20-2.64	126	158	0.96	0.66-1.40
183.4 - 275.8	132	171	1.24	0.84-1.85	83	102	1.32	0.86-2.02	121	129	1.12	0.75-1.66
≥275.9	145	219	1.33	0.87-2.04	90	92	1.59	0.99-2.56	94	92	1.31	0.84-2.06
Mean	247.7	249.6			221.6	212.1			217.1	206.7		
LIGNANS (μg/day)												
Matairisinol												
<18.1	77	130	1.00		93	130	1.00		107	142	1.00	
18.1 - 30.3	123	158	1.42	0.95-2.11	86	106	1.17	0.78-1.77	125	139	1.20	0.83-1.73
30.4 - 49.3	120	181	1.19	0.79-1.79	95	103	1.37	0.89-2.11	148	118	1.71*	1.17-2.49
≥49.4	133	206	1.21	0.79-1.85	105	105	1.48	0.94-2.31	60	92	0.88	0.56-1.40
Mean	40.7	44.0			40.6	39.8			33.2	33.0		

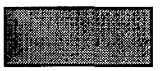
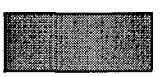
n=2,901	LATINAS				AFRICAN-AMERICANS				WHITES			
	Cases n=453	Controls n=675	OR [a]	95% CI	Cases n=379	Controls n=444	OR [a]	95% CI	Cases n=440	Controls n=491	OR [a]	95% CI
Secoisolaricirisinol												
<75.2	76	113	1.00		139	191	1.00		80	98	1.00	
75.2 - 122.1	119	186	1.07	0.72-1.60	118	103	1.59*	1.10-2.29	101	114	1.06	0.70-1.60
122.2 - 175.4	95	202	0.69	0.46-1.05	66	86	1.03	0.67-1.57	112	114	1.24	0.82-1.87
≥175.5	163	174	1.48	0.98-2.23	56	64	1.08	0.68-1.70	147	165	1.12	0.75-1.66
Mean	161.3	144.9			114.0	109.5			152.4	154.0		
Total Lignans												
<103.6	64	120	1.00		129	178	1.00		88	104	1.00	
103.6 - 159.1	131	186	1.42	0.94-2.13	113	104	1.48*	1.02-2.15	105	113	1.07	0.71-1.60
159.2 - 222.8	104	180	1.15	0.75-1.76	70	91	1.08	0.71-1.65	126	131	1.13	0.76-1.67
≥222.9	154	189	1.70*	1.11-2.60	67	71	1.18	0.75-1.88	121	143	1.02	0.68-1.52
Mean	202.0	188.9			154.6	149.3			185.7	186.9		
Total Phytoestrogens												
<1337.2	89	160	1.00		129	158	1.00		82	84	1.00	
1337.2 - 2030.2	105	162	1.03	0.70-1.51	78	89	1.10	0.73-1.65	133	152	0.89	0.60-1.33
2030.3 - 3264.5	133	164	1.39	0.93-2.06	90	103	1.03	0.68-1.56	127	136	1.01	0.66-1.55
≥3264.6	126	189	1.27	0.84-1.92	82	94	0.98	0.61-1.56	98	119	0.85	0.54-1.35
Mean	3231.5	3309.8			3058.8	3127.6			3213.8	3526.9		

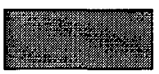
[a] Adjusted for age, education, family history of breast cancer, prior biopsy for benign breast disease, age at menarche, parity, lifetime breast-feeding, caloric intake, composite variable of menopausal status - BMI - HRT.

Table 30: Prevalence of phytoestrogen intake among controls

	CONTROLS		
	LATINAS	**AFRICAN-AMERICANS**	**WHITES**
	n=675	**n=444**	**n=491**
Total phytoestrogen intake (μg/day)			
<137.2	24%	36%	17%
≥3264.5	28%	21%	24%

Table 31: Summary of the exposure prevalence of risk and protective factors among controls, by race/ethnicity

	RISK	LATINAS	AFRICAN-AMERICANS	WHITES
RISK FACTORS				
High education	⇑			
Family history of breast cancer	⇑			
Prior biopsy for benign breast disease	⇑			
Late natural menopause	⇑			
Nulliparous	⇑			
Late first full-term pregnancy	⇑			
Pre: Tall height	⇑			
Post: Tall height	⇑			
Post: High BMI	⇑			
Post: High weight gain	⇑			
High caloric intake	⇑			
High alcohol intake	⇑			

	RISK	LATINAS	AFRICAN-AMERICANS	WHITES
PROTECTIVE FACTORS				
Foreign-born	⇓			
Late menarche	⇓			
High parity	⇓			
Pre: **long breast-feeding**	⇓			
Post: **long breast-feeding**	⇓			
Pre: **High BMI**	⇓			
Pre: **High weight gain**	⇓			
Pre: **High physical activity**	⇓			
Post **High physical activity**	⇓			

 High exposure prevalence

 Intermediate exposure prevalence

 Low exposure prevalence

Table 32: Summary of factors associated with increased breast cancer risk

n=1,912	LATINAS	AFRICAN-AMERICANS	WHITES
	OR [a] 95% CI	OR [a] 95% CI	OR [a] 95% CI
College graduate	1.32 0.84-2.07	0.92 0.56-1.50	1.27 0.66-2.44
Family history of breast cancer	1.83 1.20-2.80	1.10 0.74-1.64	1.34 0.95-1.91
Prior biopsy for benign breast disease	1.11 0.76-1.61	1.19 0.82-1.72	1.36 0.98-1.89
Natural menopause at age ≥55	3.96 1.72-9.11	0.47 0.20-1.09	2.66 1.03-6.90
Nulliparous	1.33 0.80-2.22	1.30 0.82-2.07	0.93 0.61-1.40
First-full-term pregnancy at age ≥30	1.03 0.63-1.69	1.31 0.71-2.43	0.60 0.32-1.11
Pre: Height ≥164 cm	1.18 0.62-2.27	1.39 0.61-3.18	2.83 1.14-7.05
Post: Height ≥163 cm	1.41 0.85-2.34	1.39 0.81-2.39	1.27 0.80-2.01
Caloric intake ≥2366/day	1.23 0.87-1.74	1.37 0.95-1.98	0.87 0.60-1.28
Alcohol consumption ≥10 g/day	1.11 0.65-1.90	1.22 0.74-1.99	1.30 0.86-1.98

Table 33: Summary of factors associated with decreased breast cancer risk

n=1,912	LATINAS	AFRICAN-AMERICANS	WHITES
	OR [a] 95% CI	OR [a] 95% CI	OR [a] 95% CI
Foreign born	0.63 0.47-0.84	0.63 0.24-1.66	1.02 0.63-1.64
Menarche at age ≥14	0.64 0.45-0.91	0.83 0.55-1.25	0.72 0.48-1.10
Parity ≥5	0.54 0.35-0.81	0.90 0.57-1.42	1.06 0.60-1.88
Pre: Lifetime breast-feeding ≥12 mon	1.13 0.57-2.24	0.76 0.34-1.70	0.37 0.14-0.97
Post: Lifetime breast-feeding ≥12 mon	0.65 0.41-1.02	0.96 0.61-1.53	0.73 0.45-1.18
Pre: BMI > 30	0.53 0.29-0.99	0.80 0.39-1.67	0.67 0.33-1.38
Pre: Waist-to-hip ratio ≥0.83	0.69 0.36-1.34	0.98 0.44-2.20	0.53 0.19-1.52
Pre: Weight gain ≥20.7 kg	1.29 0.55-3.03	0.60 0.21-1.73	0.39 0.10-1.45
Pre: Physical activity ≥20.8 hrs/wk	0.73 0.42-1.28	0.68 0.35-1.34	0.76 0.36-1.61
Post: Physical activity ≥20.8 hrs/wk	0.81 0.54-1.22	0.71 0.47-1.07	0.91 0.60-1.41
≥7 hrs/wk outdoors at age 25-30	1.27 0.73-2.20	0.55 0.28-1.08	0.65 0.30-1.39
Light natural skin pigmentation	0.81 0.59-1.12	0.81 0.57-1.15	0.70 0.50-0.98

Table 34: Relative attributable risk factions (RAR) among women aged 35-49, Comparing Latinas to Whites, and African-Americans to Whites: RAR for individual factors

	Multivariate odds ratios [1]		Prev W %	Prev AA %	Prev L %	RAR L vs W %	RAR AA vs W %
Country of birth							
US-born	1.0		91	95	33	23	-25
Foreign-born	0.87	0.58-1.30	9	5	67		
Education							
<12 years	1.0		2	11	49	50	6
High school graduate	1.49	0.91-2.46	16	21	18		
Some college/vocational school	1.65	1.03-2.65	33	47	20		
College graduate	1.50	0.89-2.54	49	21	13		
Family history of breast cancer							
No	1.0		85	89	95	3	2
Yes	1.10	0.70-1.72	15	11	5		
Biopsy for benign breast disease							
No	1.0		93	89	93	1	-14
Yes	1.79	1.15-2.78	7	11	7		
Age at menarche							
8-11	1.0		19	26	24	1	-5
12-13	0.91	0.65-1.26	58	54	48		
≥14	0.81	0.54-1.21	23	20	28		
Parity [2]							
0	1.30	0.90-1.89	28	14	8	37	24
1-2	1.0		51	58	35		
3-4	0.80	0.57-1.12	18	24	42		
≥5	0.84	0.46-1.51	3	4	15		
Age at first full-term pregnancy [3]							
<20	1.0		5	32	33	34	41
20-24	1.29	0.86-1.92	22	30	32		
25-29	1.25	0.79-2.00	18	15	15		
≥30	1.25	0.75-2.07	27	10	11		
Nulliparous	1.69	1.04-2.74	28	14	8		
Lifetime breast-feeding [4]							
Nulliparous	1.18	0.77-1.82	28	14	8	23	-19
Never	1.0		15	46	20		
<12 months	0.97	0.67-1.40	25	24	31		
≥12 months	0.61	0.41-0.91	33	16	41		

	Multivariate odds ratios [1]	Prev W %	Prev AA %	Prev L %	RAR L vs W %	RAR AA vs W %
Menopausal status						
Premenopausal	1.0	77	73	80	-8	-2
Postmenopausal	0.63 0.42-0.95	10	24	15		
Unknown	0.44 0.22-0.88	13	3	5		
Height (tertiles) [5]						
Low	1.0	21	14	52	45	-14
Medium	1.57 1.09-2.26	33	33	33		
High	1.72 1.17-2.52	46	53	15		
Body mass index [6]						
≤25	1.0	49	23	18	28	38
25.1-30	0.78 0.55-1.11	23	28	38		
≥30.1	0.70 0.50-0.99	28	49	44		
Waist-to-hip ratio (tertiles)						
Low	1.0	56	29	24	20	21
Medium	0.74 0.51-1.07	28	29	38		
High	0.85 0.57-1.27	16	42	38		
Weight gain (tertiles)						
Low	1.0	42	20	27	2	15
Medium	0.96 0.65-1.43	29	28	43		
High	0.86 0.50-1.45	29	52	30		
Caloric intake (tertiles)						
Low	1.0	42	37	26	-10	-9
Medium	0.87 0.63-1.25	36	31	33		
High	1.15 0.81-1.63	22	32	41		
Alcohol consumption (g/day)						
0	1.0	19	30	42	-1	-2
0.1-4.9	0.94 0.67-1.33	44	46	45		
5.0-9.9	0.73 0.41-1.29	14	9	6		
≥10.0	1.13 0.71-1.80	23	15	7		
Lifetime physical activity (tertiles)						
Low	1.0	40	38	27	13	-2
Medium	0.93 0.67-1.28	31	36	33		
High	0.69 0.49-0.98	29	26	40		

1 Odds ratios adjusted for age, education, foreign-born, family history of breast cancer, biopsy for benign breast disease, age at menarche, parity, age at first full-term pregnancy, lifetime breast-feeding, height, body mass index, physical activity, menopausal status, age at menopause.

2 Odds ratios adjusted for above variables, except age at first full-term pregnancy and breast-feeding.

3 Odds ratios adjusted for above variables, except parity and breast-feeding.

4 Odds ratios adjusted for above variables, except parity and age at first full-term pregnancy.

5 Odds ratios adjusted for above variables, except body mass index.

6 Odds ratios adjusted for above variables, except height.

Table 35: Relative attributable risk factions (RAR) among women aged 35-49, Comparing Latinas to Whites, and African-Americans to Whites: RAR for combinations of factors

Risk factors [1]	RAR L vs W %	RAR AA vs W %
Education **Country of birth**	71	3
Education **Country of birth** **Parity**	88	6
Parity **Age at first full-term pregnancy**	57	45
Parity **Breast-feeding**	24	-17
Education **Parity** **Age at first full-term pregnancy**	77	30
Country of birth **Parity** **Age at first full-term pregnancy**	79	3
Height **Waist-to-hip ratio**	64	31
Height **Body mass index**	48	-17
Body mass index **Waist-to-hip ratio**	38	43
Body mass index **Physical activity**	40	34

[1] Categorization of risk factors in RAR estimates:

Country of birth:	US-born, foreign-born
Education:	<12 years, ≥12 years
Parity:	0, 1-2, ≥3
Age at first full-term pregnancy:	<20, ≥20, nulliparous
Breast-feeding:	<12 months, ≥12 months
Height:	low, medium/high
Body mass index::	low, medium/high
Waist-to-hip ratio:	low, medium/high
Physical activity	low/medium, high

Table 36: Relative attributable risk factions (RAR) among women aged 50-79, Comparing Latinas to Whites, and African-Americans to Whites: RAR for individual risk factors

	Multivariate odds ratios [1]	Prev W %	Prev AA %	Prev L %	RAR L vs W %	RAR AA vs W %
Country of birth						
US-born	1.0	91	98	31	57	-9
Foreign-born	0.62 0.47-0.82	9	2	69		
Education						
<12 years	1.0	7	23	61	3	<1
High school graduate	0.90 0.67-1.20	22	25	19		
Some college/vocational school	1.10 0.83-1.45	34	35	14		
College graduate	0.99 0.72-1.36	37	16	6		
Family history of breast cancer						
No	1.0	84	85	92	8	<1
Yes	1.47 1.14-1.90	16	15	8		
Biopsy for benign breast disease						
No	1.0	76	80	85	1	<1
Yes	1.05 0.83-1.31	24	20	15		
Age at menarche						
8-11	1.0	21	19	19	5	4
12-13	0.83 0.66-1.05	54	50	44		
≥14	0.68 0.52-0.89	25	31	37		
Parity [2]						
0	1.18 0.86-1.62	15	10	4	34	18
1-2	1.0	42	35	22		
3-4	0.81 0.65-1.01	34	33	35		
≥5	0.63 0.48-0.84	9	22	38		
Age at first full-term pregnancy [3]						
<20	1.0	12	39	26	12	12
20-24	1.04 0.81-1.34	33	36	36		
25-29	1.12 0.83-1.52	26	10	21		
≥30	1.06 0.74-1.52	14	5	13		
Nulliparous	1.45 1.02-2.06	15	10	4		
Lifetime breast-feeding [4]						
Nulliparous	1.22 0.89-1.68	15	10	4	21	4
Never	1.0	39	45	29		
<12 months	0.89 0.70-1.13	26	23	24		
≥12 months	0.73 0.57-0.94	20	21	43		

	Multivariate odds ratios [1]	Prev W %	Prev AA %	Prev L %	RAR L vs W %	RAR AA vs W %
Age at menopause						
<45 years	1.0	27	40	31	3	-4
45-54	1.09 0.87-1.38	52	37	52		
≥55	1.64 1.12-2.41	7	11	6		
Unknown age at menopause	1.48 0.89-2.47	4	4	4		
Premenopausal	0.81 0.43-1.53	6	6	5		
Unknown menopausal status	1.12 0.54-2.34	5	1	2		
Height (tertiles) [5]						
Low	1.0	20	13	59	19	-4
Medium	1.24 0.97-1.59	32	38	31		
High	1.24 0.95-1.63	48	49	11		
Body mass index [6]						
≤25	1.0	38	17	16	1	-1
25.1-30	0.95 0.74-1.22	32	30	41		
≥30.1	1.00 0.78-1.28	30	53	43		
Waist-to-hip ratio (tertiles)						
Low	1.0	49	21	28	1	-1
Medium	0.96 0.75-1.22	30	34	36		
High	1.01 0.79-1.31	21	45	36		
Weight gain (tertiles)						
Low	1.0	35	15	29	-2	-5
Medium	1.12 0.89-1.41	36	32	42		
High	1.10 0.86-1.40	29	54	29		
Caloric intake (tertiles)						
Low	1.0	38	43	22	-8	-1
Medium	1.06 0.84-1.33	41	28	31		
High	1.16 0.91-1.47	21	28	47		
Alcohol consumption (g/day)						
0	1.0	25	49	49	11	9
0.1-4.9	0.87 0.70-1.08	46	36	40		
5.0-9.9	0.88 0.61-1.27	11	8	6		
≥10.0	1.44 1.05-1.98	18	7	5		
Lifetime physical activity (tertiles)						
Low	1.0	40	33	27	8	5
Medium	0.85 0.68-1.06	35	34	31		
High	0.79 0.62-0.99	24	33	41		

1 Odds ratios adjusted for age, education, foreign-born, family history of breast cancer, age at menarche, parity, lifetime breast-feeding, height, physical activity, age at menopause

2 Odds ratios adjusted for above variables, except age at first full-term pregnancy and breast-feeding.

3 Odds ratios adjusted for above variables, except parity and breast-feeding.

4 Odds ratios adjusted for above variables, except parity and age at first full-term pregnancy.

5 Odds ratios adjusted for above variables, except body mass index.

6 Odds ratios adjusted for above variables, except height.

Table 37: Relative attributable risk factions (RAR) among women aged 50-79, Comparing Latinas to Whites, and African-Americans to Whites: RAR for combination of factors

Risk factors [1]	RAR L vs W %	RAR AA vs W %
Parity **Age at first full-term pregnancy**	23	9
Parity **Breast-feeding**	33	12
Parity **Breast-feeding** **Country of birth**	81	2
Parity **Breast-feeding** **Height**	44	6
Parity **Breast-feeding** **Alcohol**	28	51
Height **Physical activity**	24	-1

[1] Categorization of risk factors in RAR estimates:

Country of birth:	US-born, foreign-born
Education:	<12 years, ≥12 years
Parity:	0, 1-2, ≥3
Age at first full-term pregnancy:	<20, ≥20, nulliparous
Breast-feeding:	<12 months, ≥12 months
Height:	low, medium/high
Body mass index::	low, medium/high
Waist-to-hip ratio:	low, medium/high
Physical activity	low/medium, high
Alcohol:	<10, ≥10 g/d

3. KEY RESEARCH ACCOMPLISHMENTS

Key research accomplishments achieved during the 5-year project include:

- Ascertained African-American and White breast cancer patients through the population-based San Francisco Bay area cancer registry and matched population controls through random digit dialing.
- Developed and pilot-tested a structured questionnaire that assessed a wide array of lifestyle factors. Developed an innovative methodology to assess lifetime physical activity that incorporated frequency, duration, and intensity of physical activity from multiple sources.
- Completed collection of extensive interview data and body measurements for 640 cases (313 African-Americans, 327 Whites) and 760 controls (370 African-Americans, 390 Whites), through telephone interviews and home visits. Completed data entry and data cleaning.
- Combined data with those collected with funds from the National Cancer Institute and the California Breast Cancer Research Program (total of 1326 cases and 1657 controls). Created exposure variables and analytic data files.
- Added phytoestrogen and vitamin D values to the nutrient database.
- Completed all statistical analyses corresponding to the specific aims of the project. Produced 35 tables to present results in Final Report.
- Published findings on the relation of phytoestrogens and breast cancer risk.
- Started preparation of several manuscripts.

4. REPORTABLE OUTCOMES

4.1. Published manuscripts (Appendix 1)

Horn-Ross PL, John EM, Lee M, Stewart SL, Koo J, Sakoda LC, Shiau AC, Goldstein J, Davis P, Perez-Stable EJ. Phytoestrogen consumption and breast cancer risk in a multiethnic population: the Bay Area Breast Cancer Study. Am J Epidemiol 2001;154:434-441.

4.2. Presentations

Dr. John participated in the Department of Defense Breast Cancer Research Program Meeting 'Era of Hope' in June 2000 and presented a poster and platform presentation on "Breast cancer risk factors in a multi-ethnic population".

4.3. Manuscripts in preparation

Several manuscripts are currently in preparation that include data from the DOD-funded component of the case-control study:

Davis A, John EM, Horn-Ross PL, Koo J. Lifetime occupational history and breast cancer risk: The San Francisco Bay Area Breast Cancer Study.

John EM, Horn-Ross PL, Koo J. Lifetime physical activity and breast cancer risk in pre-menopausal women: The San Francisco Bay Area Breast Cancer Study.

John EM, Horn-Ross PL, Koo J. Lifetime physical activity and breast cancer risk in post-menopausal women: The San Francisco Bay Area Breast Cancer Study.

John EM, Koo J. Physical activity patterns in a multiethnic population of women.

John EM, Koo J, Horn-Ross PL. Menstrual and reproductive characteristics and breast cancer risk in a multiethnic population: The San Francisco Bay Area Breast Cancer Study.

4.4. NCI funding

In March 1999, Dr. John received an R01 award from the National Cancer Institute to continue the case-control study described in this report (NCI R01 CA77305, titled "Vitamin D receptor gene polymorphisms and breast cancer"). Specifically, this project collected interview data and blood or mouthwash samples for cases diagnosed between 5/1998 and 4/1999 and their matched controls. We also recontacted cases diagnosed between 5/1997 and 4/1998 and their matched controls and invited them to donate a blood or mouthwash sample. These cases and controls completed the in-person interview as part of the case-control study described in this report that was partially funded by DOD. Data and biospecimen collection for this study has now been completed. DNA samples and interview data are available for 807 cases and 907 controls. Molecular analyses and statistical analyses will be completed by December 2002.

4.5. Personnel receiving pay from DOD award

Listed below is personnel involved in the study initiated in 1996 who were partially supported by funds from the DOD award. Note that except for the Principal Investigator, none of the personnel listed below worked on the project during the entire project period from 1996 to 2001. Due to turn-over, several staff members were replaced during the course of the study.

Esther M. John, Ph.D., Principal Investigator
Pamela L. Horn-Ross, Co-Investigator
Judy Goldstein, Senior Program Manager
Alma Avila, Study Coordinator
Mylene Marquez, Research Assistant
Rogeline Amos, Project Assistant
Carol Young, Administrative Assistant
Jocelyn Koo, Biostatistician
Lori Sakoda, Epidemiologist
Ernestine Wilson, Interviewer

Linda Carter, Interviewer
Kathy Sapp, Interviewer
Jolyn Smith, Interviewer
Elaine Baca, Interviewer
Amelia Herrera, Interviewer
Sofia Ramirez, Interviewer
Guiselle Melendez, Interviewer
Natasha Flint, Interviewer
Nicole Banks, Interviewer
Anne Marie Buckley, Interviewer
Mary Smith, RDD Interviewer
Marta Zahn, RDD Interviewer
Paula Blacona, RDD Interviewer
Ivonne Barrett, RDD Interviewer
Gwen Howard, Data entry technician
Charles Williams, Data entry technician

5. CONCLUSIONS

We evaluated associations between breast cancer risk and a broad range of risk factors, including newly hypothesized factors (i.e., physical activity, vitamin D, and phytoestrogens) and established or suspected risk factors (i.e., personal, menstrual, reproductive, body size, and dietary factors). We evaluated these associations in Latina, African-American, and White women aged 35-79 and compared the magnitude of associations and exposure prevalence rates in these populations. We found reduced risks among physically active women in all three racial/ethnic groups, thus providing additional epidemiologic evidence for a lifestyle factor that is potentially modifiable. The data are suggestive of an association between breast cancer risk and vitamin D related exposures. The data were most consistent for White women. Confirmation of this finding in other studies is needed. Phytoestrogen intake was not associated with breast cancer risk in any of the three racial/ethnic groups included in this study.

For the risk factors we evaluated in this study, the magnitude of association was generally similar in the three racial/ethnic groups, though there are some notable exceptions. Among African-American women, there was no increased risk associated with higher education, only a week association with family history of breast cancer, and no increased risk with late natural menopause. Risk was not reduced among Whites with high parity, among premenopausal African-Americans and postmenopausal Latinas who breast-fed for 12 months or longer, and among premenopausal Latinas with high weight gain. The interpretation of these race/ethnic specific results, particularly those stratified by menopausal status, is, however, somewhat limited by sample size. The variation in odds ratios may be due to small sample size. Since we just completed interviews with an additional 434 cases and 468 controls (NCI R01 CA77305) using the same questionnaire and protocols, we will have the opportunity to re-assess these associations in a larger study population.

In contrast to the odds ratios for Latinas, African-Americans, and Whites, the exposure prevalence rates varied greatly by race/ethnicity. For some, but not all of the exposures considered here, the prevalence rates among controls paralleled the incidence rates among Latinas (lowest incidence), African-Americans (intermediate incidence), and Whites (highest incidence).

Under the assumption that odds ratios do not vary by race/ethnicity, we estimated to what extent differences in incidence rates are attributable to differences in exposure prevalence rates. We found that the risk factors evaluated in this study indeed explained some of the differences in incidence. They explained a larger portion of the difference in incidence among younger women (aged 35-49) than older women (aged 50-79), and they explained a larger portion of the difference in incidence between Latinas and Whites than between African-Americans and Whites. The high RAR for country of birth and education warrant further study in order to identify what factors underlie the associations with country of birth.

Obviously, risk factors other than those evaluated in this study are likely to play a role in the etiology of breast cancer and in explaining racial/ethnic differences in incidence rates. A number of the risk factors identified to date support the hypothesis that ovarian hormones play a central role in breast cancer etiology [Key 1988, Hulka 2001]. Factors that reduce lifetime exposure to ovarian hormones have been associated with reduced breast cancer risk. High endogenous estrogen levels have indeed been associated with increased breast cancer risk [Thomas 1997]. There is some evidence that endogenous hormone levels measured in serum or plasma vary among racial/ethnic groups. Most of these studies compared hormone levels in Western women to those in Asian populations [Bernstein 1993]. Considerably less is known about ovarian hormone levels in African-American and Latina populations. Serum estrogen levels have been associated with polymorphisms in genes involved in the sex steroid metabolism pathway [Feigelson 1998, Feigelson 2001]. It is therefore possible that racial/ethnic differences in genetic susceptibility to ovarian hormone exposure also contribute to racial/ethnic differences in incidence rates. With the data and biospecimen resources available for the multiethnic population described in this report, we will have the opportunity to explore variations in genetic susceptibility and their relation to breast cancer incidence rates that vary by race/ethnicity.

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APPENDIX 1

Horn-Ross PL, John EM, Lee M, Stewart SL, Koo J, Sakoda LC, Shiau AC, Goldstein J, Davis P, Perez-Stable EJ. Phytoestrogen consumption and breast cancer risk in a multiethnic population. The Bay Area Breast Cancer Study. Am J Epidemiol 2001;154:434-41.

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Phytoestrogen Consumption and Breast Cancer Risk in a Multiethnic Population

The Bay Area Breast Cancer Study

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Research on the relation between phytoestrogens and breast cancer risk has been limited in scope. Most epidemiologic studies have involved Asian women and have examined the effects of traditional soy foods (e.g., tofu), soy protein, or urinary excretion of phytoestrogens. The present study extends this research by examining the effects of a spectrum of phytoestrogenic compounds on breast cancer risk in non-Asian US women. African-American, Latina, and White women aged 35–79 years, who were diagnosed with breast cancer between 1995 and 1998, were compared with women selected from the general population via random digit dialing. Interviews were conducted with 1,326 cases and 1,657 controls. Usual intake of specific phytoestrogenic compounds was assessed via a food frequency questionnaire and a newly developed nutrient database. Phytoestrogen intake was not associated with breast cancer risk (odds ratio = 1.0, 95% confidence interval: 0.80, 1.3 for the highest vs. lowest quartile). Results were similar for pre- and postmenopausal women, for women in each ethnic group, and for all seven phytoestrogenic compounds studied. Phytoestrogens appear to have little effect on breast cancer risk at the levels commonly consumed by non-Asian US women: an average intake equivalent to less than one serving of tofu per week. *Am J Epidemiol* 2001;154:434–41.

breast neoplasms; ethnic groups; isoflavones; lignans; soybeans

In the United States, breast cancer incidence varies rather dramatically by ethnicity. In the San Francisco Bay Area of California, the 1997 incidence rates were highest among White women (134 per 100,000 per year), intermediate among African-American women (103 per 100,000), and lowest among Latina women (75 per 100,000) (1). Some of these ethnic differences may be explained by differences in the relative risk or prevalence of risk factors, including dietary factors, in these subpopulations. To the extent that diet is involved in the etiology of breast cancer, its effect may be mediated in part through hormonal mechanisms.

Phytoestrogens are estrogenic compounds found in plant foods or derived from plant precursors (2–5). Because of their chemical structure, phytoestrogens compete with endogenous estrogens for binding with estrogen receptors, but, once bound, they have a far weaker estrogenic potency than endogenous estrogens and thus may act in some tissues, including the breast, as antiestrogens (2, 4–9). In addition to this possible mechanism, it has been suggested that phytoestrogens reduce cancer risk through other pathways, including their effects on hormone metabolism and their antioxidant effects (2, 10, 11).

Recent research has suggested that consumption of phytoestrogen-rich foods may reduce breast cancer risk (2, 12–15). However, the epidemiologic data on this relation remain limited in scope and contain what may prove to be important inconsistencies. Most epidemiologic studies have involved Asian populations and have examined the effects of traditional soy foods (e.g., tofu), protein from soy foods, or urinary excretion of phytoestrogens on breast cancer risk (2, 12, 13, 15–18). Most studies have not examined menopausal status–specific effects, but the findings that have been reported suggest that phytoestrogens may lower risk in premenopausal women but not in postmenopausal women (12, 17). A potentially important finding for US women was the breast cancer risk reduction associated with greater urinary excretion of phytoestrogens in Australian women aged 30–84 years, among whom the level of consumption of traditional soy-based foods is low (14). This recent finding suggests that intake of phytoestrogens by non-Asian women may be sufficient to beneficially impact breast cancer risk. However, note that in this study, urine specimens were collected prior to cancer treatment but after diagnosis and therefore may not reflect the period of cancer development or preclinical progression. Our study extends

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Abbreviation: HRT, hormone replacement therapy.

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this previous research by using a nutrient database we recently developed (19) to examine the effects of a spectrum of phytoestrogenic compounds on breast cancer risk in non-Asian women in the United States.

MATERIALS AND METHODS

Study participants

This population-based case-control study was conducted in the San Francisco Bay Area. All participants were between the ages of 35 and 79 years; resided in Alameda, Contra Costa, San Francisco, San Mateo, or Santa Clara County, California; self-identified as African American, Latina, or White; spoke sufficient English or Spanish to complete the interview; and had not been diagnosed with breast cancer prior to initiation of this study. Cases were identified through the Greater Bay Area Cancer Registry, a population-based cancer registry that is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and the statewide California Cancer Registry. All breast cancer cases diagnosed between April 1, 1995, and April 30, 1998, and identified to the cancer registry as White, African American, or Latina were screened by telephone to verify their race/ethnicity. Of 7,591 identified cases, 297 (4 percent) were deceased, and physicians indicated contraindications to contacting 120 (2 percent). Of 7,174 cases approached regarding screening, 6,157 (86 percent) were screened, 487 (7 percent) declined or were too ill to participate, and 530 (7 percent) were not screened for other reasons (including our inability to locate them, their not being fluent in the languages in which we were interviewing, etc.). All women who self-identified as African American or Latina, and a 10 percent random sample of those identifying as White, were invited to participate in an extensive in-person interview. Of these 1,539 women, 1,326 (86 percent) were interviewed, including 469 (88 percent) of 536 Latina women, 409 (85 percent) of 480 African-American women, and 448 (86 percent) of 523 White women. A total of 149 (10 percent) women declined to participate, and 64 (4 percent) were not interviewed for other reasons.

Controls were identified through random digit dialing. The method used was a modification of the Waksburg method, where primary sampling units were identified by using cancer registry data. By assuming that people with cancer are distributed randomly in the general population, we generated primary sampling units for each ethnic group based on the telephone numbers of all cancer patients of that ethnicity diagnosed during several recent years (regardless of sex, age, or cancer site). This method substantially improves the efficiency of locating persons of minority groups. We selected 2,389 controls, frequency matched to cases on age (5-year groups) and ethnicity (three groups), and invited them to participate in the screening interview. Of these women, 2,062 (86 percent) were screened; 168 (7 percent) declined, were too ill, or were deceased; and 159 (7 percent) were not screened for other reasons. After 89 women who did not meet the eligibility criteria were excluded (i.e., they had a history of breast cancer or were of ineligible age or race/ethnicity), 1,973 controls were invited to participate in the in-person interview. Of these 1,973 women, 1,657 (84 percent) were interviewed, including 699 (87 percent) of 808 Latina women, 460 (82 percent) of 562 African-American women, and 498 (83 percent) of 603 White women. A total of 251 (13 percent) declined to participate, and 65 (3 percent) were not interviewed for other reasons.

Data collection

In-person interviews were conducted by using a standardized, structured questionnaire that covered a wide variety of topics: demographics and language use, physical activity, sun exposure, dietary intake and vitamin and mineral supplement use, body characteristics, residential history, occupational history, menstrual and reproductive events, hormone use, and medical history. Whenever possible, phrasing of questions was drawn from established and validated instruments. Interviews were conducted in Spanish for 166 cases and 272 controls. Standard translation methodology, including forward and backward translation and review for colloquial phrasing, was used in translating all subject materials (20, 21). All study components were approved by the Institutional Review Board of the Northern California Cancer Center (Union City, California).

Dietary intake during the year prior to diagnosis (for cases) or selection (for controls) was assessed via a modified version of the Block food frequency questionnaire (22, 23). To quantify the intake of seven specific phytoestrogenic compounds, we used a nutrient database we had developed to assess phytoestrogen intake by using food frequency questionnaires (19). These seven compounds represent three classes of phytoestrogens found in plant foods: isoflavones (genistein, daidzein, formononetin, and biochanin A), coumestans (coumestrol), and lignans (matairesinol and secoisolariciresinol). A validation/calibration study of our phytoestrogen assessment and nutrient database is currently in progress. Other studies have shown that intake of soy foods or isoflavones (measured from a limited number of soy-based foods) is positively related to urinary isoflavone levels (24–27) and that vegetarian and macrobiotic dietary patterns are associated with urinary lignan excretion (28).

Data analysis

Dietary analyses were based on 1,272 (96 percent) cases and 1,610 (97 percent) controls; excluded were 54 cases and 47 controls whose daily caloric intake was judged to be under- or overreported, that is, <600 or >5,000 kcal per day, respectively. For menopausal-specific analyses, women were considered postmenopausal if their menstrual periods had stopped more than 1 year prior to diagnosis/selection and they had never used hormone replacement therapy (HRT) or had used HRT only after cessation of menses. Also included in this group were women who began using HRT prior to cessation of menses but had attained age 55 years or more at the time of diagnosis/selection. Women who had begun using HRT prior to cessation of menses but had not

attained age 55 years were excluded from these analyses because their menopausal/ovarian status could not be determined. The remainder of the women were considered premenopausal.

After initial examination of the data, we estimated odds ratios and 95 percent confidence intervals by using unconditional logistic regression analyses controlling for age, race/ethnicity, and other potentially confounding factors, as noted in the footnotes to the tables presented in this paper. For the variables used in this study, the risk estimates and confidence intervals obtained from basic models (adjusting for age, race/ethnicity, and daily caloric intake only) did not differ much from those adjusted for multiple covariates; thus, only the latter are presented.

RESULTS

Table 1 presents the association between established breast cancer risk factors and risk in this population. Increased risk was associated with early menarche, nulliparity, self-report of previous biopsy-diagnosed benign breast disease, family history of breast cancer in a first-degree female relative(s), and higher education.

The average phytoestrogen consumption was 3,174 μg per day for cases and 3,326 μg per day for controls; this difference was not statistically significant ($p = 0.46$). On average, for cases and controls, 87 and 88 percent, respectively, of total phytoestrogen consumption was from isoflavones, with tofu, doughnuts, soy milk, and white bread among the largest contributors to daily intake (also refer to Horn-Ross et al. (29)). Table 2 shows the associations of traditional soy-based foods, foods with added soy flour, and foods with added soy protein with breast cancer risk. Consumption of soy milk and soyburgers was associated with a statistically significant reduction in breast cancer risk.

Table 3 presents the associations for daily intake of the specific phytoestrogenic compounds and classes of compounds and of total phytoestrogens. Only small variations in breast cancer risk were observed, even at the highest levels

TABLE 1. Association between established breast cancer risk factors and breast cancer risk among women participating in the multiethnic Bay Area Breast Cancer Study, San Francisco, California, 1995–1998

Risk factor	Cases (n = 1,326)*	Controls (n = 1,657)*	OR†,‡	95% CI†
Age (years) at menarche				
<12	329	344	1.0	
12–13	670	825	0.83	0.69, 0.99
≥14	313	476	0.68	0.56, 0.84
Parity				
Nulliparous	217	187	1.0	
1–2	556	607	0.79	0.63, 1.0
3–4	389	546	0.62	0.49, 0.79
≥5	161	317	0.44	0.33, 0.58
Age (years) at first full-term pregnancy (parous women)				
<20	281	401	1.0	
20–24	414	531	1.1	0.92, 1.4
25–29	240	291	1.2	0.94, 1.5
≥30	156	198	1.2	0.88, 1.5
Self-report of biopsy-diagnosed benign breast disease				
Never	1,056	1,400	1.0	
Ever	264	253	1.3	1.1, 1.6
Family history of breast cancer in first-degree female relative(s)				
No	1,112	1,468	1.0	
Yes	211	189	1.4	1.2, 1.8
Education (years)				
<12	285	513	1.0	
12	266	343	1.4	1.1, 1.7
13–15	433	457	1.7	1.4, 2.1
≥16	339	344	1.8	1.4, 2.3

* Columns totaling less than the total number of cases or controls reflect missing values for those variables.
† OR, odds ratio; CI, confidence interval.
‡ Adjusted for age and race/ethnicity.

at which these compounds were consumed by these populations. Note that because of the different estrogenic (and antiestrogenic) activity of the various compounds, total intake—reported here as the sum of the various com-

TABLE 2. Association between consumption of selected soy-based foods and foods with added soy flour or protein and breast cancer risk among women participating in the multiethnic Bay Area Breast Cancer Study, San Francisco, California, 1995–1998

Food and level of consumption	Cases (n = 1,272)*	Controls (n = 1,610)*	OR†,‡	95% CI†
Traditional soy-based foods				
Nonfermented				
Tofu				
Nonconsumers	931	1,163	1.0	
<1/month	168	237	0.79	0.63, 0.99
≥1/month	173	207	0.89	0.70, 1.1
Soy milk				
Nonconsumers	1,232	1,532	1.0	
Consumers	39	78	0.57	0.38, 0.85
Fermented				
Miso soup				
Nonconsumers	1,094	1,373	1.0	
<1/month	123	137	1.1	0.81, 1.4
≥1/month	97	93	1.1	0.81, 1.5
Nontraditional soy-based foods				
Soyburgers				
Nonconsumers	1,047	1,301	1.0	
<1/month	132	174	0.79	0.62, 1.0
≥1/month	91	134	0.74	0.55, 0.99
Foods with added soy flour§				
Doughnuts				
Nonconsumers	285	340	1.0	
<1/month	203	289	0.77	0.60, 0.99
1–3/month	341	404	0.98	0.79, 1.2
≥4/month	441	577	0.99	0.80, 1.2
White bread				
Nonconsumers	211	301	1.0	
<1/week	287	397	0.98	0.76, 1.2
1–3/week	467	586	1.1	0.88, 1.4
≥4/week	305	325	1.3	1.0, 1.7
Pancakes, waffles				
Nonconsumers	230	327	1.0	
<1/month	294	399	0.90	0.71, 1.1
1–3/month	475	525	1.2	0.93, 1.4
≥4/month	273	358	1.0	0.80, 1.3
Foods with added soy protein§				
Canned tuna				
Nonconsumers	161	226	1.0	
<1/month	165	282	0.69	0.51, 0.92
1–3/month	459	568	0.95	0.74, 1.2
≥4/month	486	534	1.1	0.83, 1.4
Canned chili				
Nonconsumers	614	854	1.0	
<1/month	289	366	1.0	0.82, 1.2
≥1/month	367	389	1.2	0.99, 1.4

* Columns totaling less than the total number of cases or controls reflect missing values for those variables.
† OR, odds ratio; CI, confidence interval.
‡ Adjusted for age; race/ethnicity; age at menarche; parity; lactation; history of benign breast disease; family history of breast cancer; education; a composite variable including menopausal status, body mass index, and hormone replacement therapy use; and daily caloric intake.
§ Soy additives found in some but not all brands.

TABLE 3. Association between phytoestrogen consumption and breast cancer risk among women participating in the multiethnic Bay Area Breast Cancer Study, San Francisco, California, 1995–1998

Phytoestrogen (μg/day)	Cases (*n* = 1,272)	Controls (*n* = 1,610)	OR*,†	95% CI*
Isoflavones				
Genistein				
<480	304	402	1.0	
480–783	321	403	1.0	0.81, 1.3
784–1,439	359	402	1.2	0.92, 1.4
≥1,440	288	403	0.92	0.72, 1.2
per 100 μg/day			1.00	0.996, 1.001
Daidzein				
<473	288	402	1.0	
473–746	344	403	1.2	0.93, 1.5
747–1,222	323	402	1.1	0.87, 1.4
≥1,223	317	403	1.1	0.85, 1.4
per 100 μg/day			1.00	0.995, 1.001
Biochanin A				
<22	297	402	1.0	
22–41	323	403	1.1	0.91, 1.4
42–82	318	402	1.1	0.89, 1.4
≥83	334	403	1.2	0.85, 1.5
per 10 μg/day			1.00	0.99, 1.01
Formononetin				
<9	265	402	1.0	
9–19	318	403	1.2	0.97, 1.5
20–39	353	402	1.1	0.89, 1.4
≥40	336	403	1.2	0.96, 1.5
per 10 μg/day			1.01	0.99, 1.02
Total isoflavones				
<1,048	292	402	1.0	
1,048–1,647	332	403	1.1	0.87, 1.4
1,648–2,774	349	402	1.2	0.93, 1.5
≥2,775	299	403	1.0	0.79, 1.3
per 1,000 μg/day			0.99	0.98, 1.01

Table continues

pounds—may not be the most informative measure of biologic exposure. However, given the lack of association observed in this study, a more complex measure (e.g., one weighted by estrogenic activity) would not have produced different results. As illustrated in table 4, risk did not vary substantially by race/ethnicity or menopausal status.

DISCUSSION

Several epidemiologic studies have shown consumption of tofu, miso soup, or soy protein, or the urinary excretion of phytoestrogens (which reflect exposure in the last 24–48 hours), to be associated with a 20–75 percent reduction in breast cancer risk in Asian (2, 12, 15, 17), Asian-American (13), non-Asian North-American (30, 31), and Australian (14) populations. However, phytoestrogen exposure was not the primary focus of most of these studies, and results were often based on assessment of one or two soy-based food items. In addition, studies of non-Asian populations showed that soy foods often were consumed by only a small portion of the population, for example, by less than 3 percent of the women participating in the Iowa Women's Health Study (31). In examining similar associations, we observed a significant decrease in breast cancer risk associated with consumption of soy milk, but, as in other western populations, this beverage was consumed by only 3 percent of cases and 5 percent of controls.

Contrary to these observations, other Asian studies (16, 18) have found no association between breast cancer risk and consumption of soy protein and/or soy-based foods. Only three studies have examined the effects of soy by menopausal status, all in Asian or Asian-American women (12, 13, 17). Two of the three observed a risk reduction in premenopausal women but no effects in postmenopausal women (12, 17); the third found risk to be reduced in both groups, but the postmenopausal group in that study was restricted to women who were less than age 56 years. That

TABLE 3. Continued

Phytoestrogen (μg/day)	Cases (n = 1,272)	Controls (n = 1,610)	OR*,†	95% CI*
Coumestans				
Coumestrol				
<119	285	402	1.0	
119–182	322	403	1.1	0.90, 1.4
183–276	336	402	1.2	0.97, 1.5
≥277	329	403	1.4	1.1, 1.7
per 100 μg/day			1.03	0.98, 1.08
Lignans				
Matairesinol				
<18	277	402	1.0	
18–29	334	403	1.3	1.0, 1.6
30–49	363	402	1.3	1.1, 1.7
≥50	298	403	1.1	0.89, 1.5
per 10 μg/day			0.99	0.97, 1.02
Secoisolariciresinol				
<75	295	402	1.0	
75–121	338	403	1.2	0.96, 1.5
122–175	273	402	0.96	0.76, 1.2
≥176	366	403	1.3	1.0, 1.6
per 100 μg/day			1.08	0.99, 1.18
Total lignans				
<104	281	402	1.0	
104–158	349	403	1.3	1.0, 1.6
159–223	300	402	1.1	0.88, 1.4
≥224	342	403	1.3	1.0, 1.6
per 100 μg/day			1.06	0.98, 1.14
Total phytoestrogens				
<1,337	300	402	1.0	
1,337–2,029	316	403	1.0	0.81, 1.3
2,030–3,264	350	402	1.2	0.92, 1.5
≥3,265	306	403	1.0	0.80, 1.3
per 100 μg/day			0.99	0.98, 1.01

* OR, odds ratio; CI, confidence interval.
† Adjusted for age; race/ethnicity; age at menarche; parity; lactation; history of benign breast disease; family history of breast cancer; education; a composite variable including menopausal status, body mass index, and hormone replacement therapy use; and daily caloric intake.

is, the majority were recently postmenopausal. In the present study, we found the effects of phytoestrogens to be absent in both pre- and postmenopausal women at the levels of consumption we were examining.

Thus, there is some evidence that soy consumption may reduce the risk of breast cancer in non-Asian women; its effects may be stronger in premenopausal women, but the evidence is far from conclusive. The purpose of this study was to expand on these findings by examining 1) the effects on breast cancer risk of seven specific phytoestrogenic compounds by using our newly developed nutrient database for assessing phytoestrogen intake from a wide variety of foods (19) and 2) these associations in three non-Asian ethnic subgroups of pre- and postmenopausal women. For non-Asian women, who usually consume relatively few traditional soy-based foods, foods with added soy protein or flour (which are becoming increasingly common in the United States) and foods rich in lignans (another class of phytoestrogenic compounds that may act similarly to the isoflavones found in soy (5, 11)) may be equally important as traditional soy-based foods are in other populations.

However, our analyses showed no association between phytoestrogen exposure and breast cancer risk in this population. These findings were similar for breast cancer in both pre- and postmenopausal women and for specific phytoestrogenic compounds, classes of compounds, and total exposure. Note that the highest quartile of consumption in this population was about only 3 mg/day, a level equivalent to less than one serving of tofu per week. In contrast, the

TABLE 4. Association between total isoflavone consumption and breast cancer risk among subgroups of women participating in the multiethnic Bay Area Breast Cancer Study, San Francisco, California, 1995–1998

Subgroup and total isoflavones (μg/day)	Cases	Controls	OR*,†	95% CI*
Latina				
<1,048	91	162	1.0	
1,048–1,647	113	157	1.1	0.75, 1.6
1,648–2,774	124	167	1.2	0.80, 1.8
≥2,775	125	189	1.2	0.78, 1.8
per 1,000 μg/day			0.99	0.97, 1.02
African American				
<1,048	117	154	1.0	
1,048–1,647	86	95	1.2	0.80, 1.8
1,648–2,774	99	101	1.2	0.83, 1.9
≥2,775	77	94	1.0	0.65, 1.7
per 1,000 μg/day			0.99	0.97, 1.02
White				
<1,048	84	86	1.0	
1,048–1,647	133	151	0.89	0.60, 1.3
1,648–2,774	126	134	1.0	0.67, 1.6
≥2,775	97	120	0.82	0.52, 1.3
per 1,000 μg/day			0.99	0.96, 1.01
Premenopausal				
<1,048	59	79	1.0	
1,048–1,647	110	120	1.3	0.80, 2.0
1,648–2,774	105	143	0.95	0.59, 1.5
≥2,775	124	129	1.2	0.75, 2.0
per 1,000 μg/day			1.00	0.98, 1.02
Postmenopausal				
<1,048	219	312	1.0	
1,048–1,647	210	270	1.1	0.80, 1.4
1,648–2,774	234	241	1.4	1.0, 1.8
≥2,775	163	254	0.96	0.71, 1.3
per 1,000 μg/day			0.99	0.97, 1.01

* OR, odds ratio; CI, confidence interval.

† Adjusted for age; race/ethnicity; age at menarche; parity; lactation; history of benign breast disease; family history of breast cancer; education; a composite variable including menopausal status, body mass index, and hormone replacement therapy use; and daily caloric intake.

average intake of phytoestrogens in Asian countries has been estimated to range from about 15 to 30 mg/day. Thus, our findings do not preclude the possibility of a threshold effect with a reduction in risk limited to higher levels of exposure (such as those for Asian and Asian-American women). However, also of importance for public health and clinical recommendations is the study by Petrakis et al. (32), which observed that particularly high levels of daily phytoestrogen exposure may increase the risk of premenopausal breast cancer.

Finally, our study found no differences in the relative risk or prevalence of phytoestrogen consumption between women representing the three ethnic groups included in this study. Thus, dietary intake of phytoestrogens does not account for the lower risk of breast cancer observed among Latina women, disproving our previous hypothesis (33).

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