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Red meat, poultry, and fish intake and breast cancer risk among Hispanic and Non-Hispanic white women: The Breast Cancer Health Disparities Study

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Abstract

Purpose—There is suggestive but limited evidence for a relationship between meat intake and breast cancer (BC) risk. Few studies included Hispanic women. We investigated the association between meats and fish intake and BC risk among Hispanic and NHW women.

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Methods—The study included NHW (1,982 cases and 2,218 controls) and US Hispanics (1,777 cases and 2,218 controls) from 2 population-based case-control studies. Analyses considered menopausal status and percent Native American ancestry. We estimated pooled ORs combining harmonized data from both studies, and study and race/ethnicity specific ORs that were combined using fixed or random effects models, depending on heterogeneity levels.

Results—When comparing highest versus lowest tertile of intake, among NHW we observed an association between tuna intake and BC risk (pooled OR = 1.25; 95% CI = 1.05–1.50; trend p = 0.006),. Among Hispanics, we observed an association between BC risk and processed meat intake (pooled OR = 1.42; 95% CI 1.18–1.71; trend p < 0.001), and between white meat (OR = 0.80; 95% CI 0.67–0.95; trend p = 0.01) and BC risk, driven by poultry. All these findings were supported by meta-analysis using fixed or random effect models, and were restricted to estrogen receptor positive tumors. Processed meats and poultry were not associated with BC risk among NHW women; red meat and fish were not associated with BC risk in either race/ethnic groups.

Conclusions—Our results suggest the presence of ethnic differences in associations between meat and BC risk that may contribute to BC disparities.

Introduction

Breast cancer (BC) incidence rates vary by race/ethnicity in the United States (US). Non-Hispanic white (NHW) women have the highest age adjusted rates (128.0 per 100,000), whereas Hispanic women have among the lowest rates (93.2 per 100,000) [1]. In spite of the lower incidence rates, Hispanic women are more likely to be diagnosed at advanced disease stages and with estrogen receptor (ER) negative tumors [2, 3]. Racial/ethnic differences in the distribution of risk factors such as reproductive history, alcohol consumption, and menopausal hormone therapy use [2, 4, 5] may partially explain the disparity in incidence, but do not account for all of the observed variability [5]. While migrant studies found a rise in incidence rates of BC upon immigration to the US from countries with traditionally low BC incidence rates, such as Latin America and Asia [4, 6], consideration of known risk factors do not fully explain the observed rate differences between US and foreign-born Hispanic women [4]. Differences in the frequency of predisposing genetic variants may also play a role. Hispanics are a genetically admixed population made up of European, Native American (NA), and African ancestry components. Higher European ancestry is associated with increased BC risk in both US Hispanic and Mexican women [7, 8], and BC susceptibility loci were identified among Latinas via admixture mapping, and more recently, through genome-wide association analyses [9, 10]. Altogether, the current evidence suggests the presence of unmeasured or poorly characterized BC risk factors might be particularly relevant for Latina women, a growing population.

Diet, particularly meat intake, has not been considered in investigations of BC among Latina women. The World Cancer Research Fund and the American Institute for Cancer Research recommend limiting red and processed meat intake based on conclusive links between meat intake and colorectal cancer [11]. Epidemiological evidence for positive associations between intakes of meat, poultry, and fish and BC risk is less conclusive, but suggestive [11, 12]. Possible mechanisms include oxidative damage from bioavailable heme-iron [13], exposure to exogenous growth-promoting hormones used in animal food production [14],

and intake of mutagenic xenobiotic compounds such as heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs), and N-Nitroso compounds (NOCs) [15, 16]. Meta-analyses of large prospective studies yielded weakly positive associations that failed to reach statistical significance [17, 18]. In contrast, another meta-analysis including cohort and case-control studies performed on pre-menopausal women reported positive summary associations between meat intake and BC risk [19], although there is substantial heterogeneity across studies regarding the choice of model covariates and control selection. In addition, genetic variants may modify the association with meat intake. To date, several studies have investigated variants in mutagen metabolism, with two reporting significant interactions with meat intake [20, 21].

In this study we investigated the association between meat, poultry, and fish intake and BC risk among NHW and US Hispanic women. Our goals were to understand the role of meat/fish intake in BC risk and its potential impact on the observed BC incidence rate disparity.

Methods

Study population

The Breast Cancer Health Disparities Study (BCHD) [22] is a consortium of three case-control studies (two from the US and one from Mexico). In this analysis we included data from the two population-based US case-control studies: the 4-Corners Breast Cancer Study (4-CBCS), and the San Francisco Bay Area Breast Cancer Study (SFBCS). Protocols were approved by the Institutional Review Board for Human Subjects at each institution, and all participants signed written informed consents prior to study enrollment.

4-Corners Breast Cancer Study (4-CBCS)—This study consists of NHW, Hispanic, or NA women aged 25–79 years who resided in non-reservation areas within the states of Arizona, Colorado, New Mexico, or Utah at the time of diagnosis (cases) or selection into the study (controls) [23]. State tumor registries were used to identify cases and confirm eligibility criteria, which included a histologically confirmed diagnosis of in situ or invasive breast cancer between October 1999 and May 2004. Information on tumor ER/PR status was also obtained from registry data as indicated in pathology reports. Controls were selected within target populations from sources ranging from commercial mailing lists to driver's license lists, and frequency matched on ethnicity and 5-year age distribution of cases. Participation rates were 63% and 36% for Hispanic cases and controls, respectively, and 71% and 47% for NHW cases and controls, respectively. Trained interviewers administered a structured computerized questionnaires in English or Spanish to collect participant information up to the reference year (the year prior to diagnosis for cases or selection for controls). Dietary intake was assessed using a computerized version of a validated dietary history questionnaire (CARDIA) which captures more than 300 food items [24] and was modified to accommodate foods commonly eaten in the Southwestern US [25]. Weight and height were measured at the time of interview. Of those interviewed, blood for DNA extraction was collected from 76.6% of cases and 82.4% of controls.

San Francisco Bay Area Breast Cancer Study (SFBCS)—Participants in SFBCS were NHW, Hispanic, and African American women ages 35–79 years newly diagnosed

with a first primary histologically confirmed invasive breast cancer between April 1995 and April 2002 for Hispanic women and between April 1995 and April 1999 for NHW and African American women who resided in the San Francisco Bay Area at the time of diagnosis (counties of San Francisco, San Mateo, Santa Clara, Alameda, and Contra Costa) [4, 26]. Cases were ascertained via the Greater Bay Area Cancer Registry and screened by telephone for self-reported race/ethnicity and study eligibility (89% participation among those contacted). Information on tumor ER/PR status was obtained from registry data as indicated in pathology reports. All eligible Hispanic and African American women and a 10% random sample of eligible NHW women were invited to participate in an in-person interview. Controls residing in the San Francisco Bay Area were selected via random-digit dialing using the Waksberg method, and frequency matched to cases by race/ethnicity and 5 year age group. They were also screened by telephone for self-reported race/ethnicity and study eligibility (92% participation among those contacted). Among those eligible for the in-person interview, participation rates were 89% and 88% for Hispanic cases and controls, respectively, and 86% and 83% for NHW cases and controls, respectively. Trained bilingual interviewers administered a structured questionnaire to collect participant information up to the reference year (the calendar year prior to diagnosis for cases or selection for controls). Height and weight were measured in person. Dietary intake during the reference year was assessed using a modified version of the Block's Health History and Habits Questionnaire which captured 85-food items [27]. A biospecimen component was added to the investigation in 1997, and among those eligible, 93% of cases and 92% of controls contributed a blood or mouthwash sample.

We excluded 158 individuals with missing or extreme caloric intake, defined as daily intake of < 600 or > 6,000 kcal, 301 individuals with in situ BC diagnosis or for whom BC was not the first primary cancer diagnosis, and 128 individuals who self-identified as American Indian/Native American. Prior to further exclusions, there were 8,242 study participants: 2,064 cases and 2,392 controls from 4-CBCS, and 1,695 cases and 2,091 controls from SFBCS. DNA for genotyping was available for 5,544 participants (~ 67.3%); thus analyses adjusted for or stratified by admixture information were performed on this smaller subset. Lastly, participants with missing covariate or exposure data were dropped from the final fitted models. The final main effects models included 7,470 participants, whereas final models utilizing genetic data included 5,079 participants.

Data Harmonization and exposure variables

Adjustment variables—Data were harmonized across the two studies. Adjustment variables included body mass index (BMI), calculated as self-reported weight (kg) divided by height (m) squared. Race/ethnicity was self-reported. Age corresponds to age during the reference year. Education was defined as the highest educational level attained (less than high school, high-school/GED, post-high school). Reports of history of first-degree relative with breast cancer were dichotomized (yes/no). Parity was defined as the number of live and stillborn births (0, 1–2, 3–4, 5+ births) while age at first birth was defined as age at first live or still birth. These were combined into a single reproductive history variable (nulliparous, < 20, 20–24, 25–29, 30 years). Lifetime physical activity was scored from 1 (low) to 4 (high), based on study-specific cut-points for hours per week of vigorous activity during the

reference year, and at ages 15, 30, and 50. Women were classified as pre-menopausal or post-menopausal based on responses to menstrual history questions. All women who reported having periods during the referent year were classified as pre-menopausal. Women taking menopausal hormone therapy and still having periods were classified as post-menopausal if their age was above the 95th percentile of age distribution among women reporting natural menopause (no periods for 12 months) within their corresponding race/ethnicity groups and study center. This age cutoff varied by study: 58 years for NHWs and 56 for Hispanics in 4-CBCS, and 55 for NHWs and 56 for Hispanics in the SFBCS. Alcohol intake (gm/day) was calculated based on lifetime consumption in 4-CBCS and consumption during the reference year in SFBCS, and was categorized as none, <5, 5 to <10, and 10. Lastly, dietary variables included in the adjusted models were daily caloric intake (kcal/day), and nutrient-density adjusted daily intake of fiber and total fat (g/kcal/day).

Meat/fish Consumption—In order to harmonize meat/fish intake variables across studies, we combined each studies' questionnaire meat items into six categories: red meat, processed meat, white meat (combined poultry and fish intake), poultry, fish, and tuna. Both questionnaires included similar meat items for each category. Red meat includes items such as beef steaks, burgers, roasts, veal, ribs, pork (chops, steaks, roasts, ribs, fresh hams), lamb, and any dishes that included fresh meat as an ingredient. Processed meats include hotdogs, sausages, bacon, luncheon meats, processed ham, and any dishes that included these items. Chicken and turkey make up the poultry category, while fish includes any seafood items, such as white and dark fishes, and shellfish. White meat is a combination of all poultry and fish intake. While the fish variable includes tuna intake, we chose to analyze tuna separately since questionnaires contained questions specific for tuna and dishes containing tuna. As caloric intake could confound associations between meat and BC, the combined meat/fish variables were adjusted for energy intake using the nutrient density method [28], and are expressed as grams per 1,000 kcal of energy intake per day. Lastly, using the nutrient density adjusted variables we categorized intake levels by calculating study- and race/ethnicity-specific tertiles based on distributions of energy-adjusted meat/fish intake among controls, then combining corresponding tertile levels across studies and race-ethnic groups. For tuna intake, a substantial number of controls (> 10%) reported zero intake during the referent period. These participants were grouped into the lowest tertile group, while the rest were split into the second and third tertile groups based on median levels of intake among controls.

Ancestry Informative Markers

Genotyping (Goldengate Chemistry, San Diego, CA) was performed as part of a larger effort to investigate the association between variants in genes related to inflammation, hormones, and energetic factors and BC risk in the BCHD Study [22]. We obtained genotype information for 104 Ancestry Informative Markers (AIMs), which were used to categorize women based on percent level of NA ancestry, also previously described [22]. Briefly, using the program STRUCTURE 2.0, individual ancestry for each study participant was estimated assuming two founding populations (European and NA). A three founding population model was assessed, but did not fit the population structure with the same level of repeatability and correlation among runs. Ancestry is expressed as percent Native American.

Statistical Analysis

Distributions of covariates by race/ethnicity were summarized using frequencies (proportions) and means (standard deviations), and group differences were assessed using Chi-square and Student's t-tests, respectively. Measures of association between overall meat/fish intake in tertile categories and BC risk were calculated using unconditional logistic regression models. Covariates included age, study center, menopausal status (when not stratified), family history of BC, education, alcohol consumption, parity/age at first birth, physical activity, BMI during reference year, daily caloric intake, intake of fiber, and total fat. Oral contraceptive (never/ever) were accounted for in analyses among pre-menopausal women, and hormone replacement therapy use (never/ever) were accounted for in post-menopausal analyses and analyses of all women combined, but neither significantly change estimates (< 10% change), and thus were omitted from the final results. Trend tests were performed by modeling the indicator variables continuously; median levels of intake are not meaningful given the manner in which the variables were harmonized. All analyses were stratified by race/ethnicity and menopausal status. Among Hispanic women, analyses were stratified by admixture tertile categories which were calculated based on the distribution of NA ancestry among Hispanic controls. Tests of heterogeneity of odds ratios by menopausal status, race/ethnicity, and admixture categories were computed using likelihood ratio tests of models including and excluding interaction terms between these variables and meat/fish intake. Sub-analyses included mutual adjustment for other meat, poultry, and fish intake variables. Lastly, multinomial logistic regression was used to model the risk of BC by tumor estrogen receptor status, with controls serving as the reference group.

As mentioned previously, 4-CBCS and SFBCS employed different instruments to measure dietary intake, leading to study differences in daily intake values of meat and fish. To address this, we calculated study- and race/ethnicity-specific tertiles. To further address any potential heterogeneity across studies, we performed additional analyses to combine study-specific odds ratios for each racial/ethnic group. We obtained these combined ORs by using random [29] or fixed effects models depending on the level of study heterogeneity as determined by Cochrane's Q [29] and I^2 [30] statistics. Specifically, among NHW women the Cochran Q was < 0.05 or I^2 > 50%, thus random effects models were employed exclusively. There were less study heterogeneity among Hispanic women, with Cochran Q > 0.05 and I^2 < 50%, with the exception of poultry intake. Therefore, combined odds ratios for all variables, except poultry, were obtained using fixed effect models, whereas for poultry intake random effects models were used. We also obtained combined ORs stratified by estrogen receptor status. We first calculated study and race specific results for each breast cancer subtype (ER+ and ER) compared to controls using unconditional logistic regression, then combined these results using random/fixed effects models, as above.

All hypothesis tests were two-sided. Analyses were performed using the statistical software STATA SE 12.0 (STATA Corporation, College Station, TX).

Results

Characteristics of study participants stratified by race/ethnicity are summarized in Table 1. Overall, NHW cases and controls were older than Hispanic cases and controls, and were

more likely to have a first degree family history of breast cancer. In addition, NHW cases and controls consumed more alcohol, were more often nulliparous and older at first birth, were more likely to use oral contraceptives and undergo hormone replacement therapy, and attained higher levels of education than Hispanic cases and controls, whereas the latter had higher BMI and daily caloric intake levels. Compared to controls, both NHW and Hispanic cases were more likely to have a first degree family history of BC, consume more alcohol, and be nulliparous. Among Hispanics, higher education levels and older age at first birth were associated with BC risk, while higher BMI was inversely associated with BC risk. In general, Hispanic women consumed less meats and fish than NHW women, with the exception of processed meat, for which consumption was lower among Hispanic women in SFBCS and higher in 4-CBCS.

Meat/fish variables and BC risk among NHW and Hispanic women

We investigated the association between six meat/fish variables and BC risk among NHW women (Table 2) and among Hispanic women (Table 3), stratifying by menopausal status, pooling data from both case-control studies. Among NHW women, tuna intake was the only meat/fish variable associated with BC risk (T3 vs. T1 OR = 1.25; 95% CI 1.05–1.50), with comparable OR estimates for pre- and post-menopausal women (Table 2). We observed a similar association between high intake of tuna and BC risk among Hispanic women (overall T3 vs. T1 OR = 1.21; 95% CI 1.02–1.44) (Table 3), with a significant association among post-menopausal women only (T3 vs. T1 OR = 1.29, 95% CI 1.04–1.61); however, there was no evidence of statistically significant heterogeneity by menopausal status. In contrast, among Hispanics, high intake of processed meats was associated with increased BC risk (T3 vs. T1 OR = 1.42; 95% CI 1.18–1.71), with similar results for pre- and post-menopausal women. The observed difference in ORs associated with processed meats intake between NHW and Hispanic women was statistically significant (2df heterogeneity p value = 0.03; data not shown). Among Hispanic women, we also observed an inverse association between high poultry intake and BC risk (T3 vs. T1 OR = 0.80; 95% CI 0.67–0.95) (Table 3). The inverse association was limited to pre-menopausal women, but there was no evidence of statistically significant heterogeneity by menopausal status. Furthermore, there was no evidence of effect modification of association between poultry and BC risk by race. Similarly, we observed an inverse association between high white meat intake and BC risk (T3 vs. T1 OR = 0.80; 95% CI 0.67–0.95), with no significant heterogeneity by menopausal status (Table 3). Mutual adjustment for other meat/fish intake variables did not drastically change estimates.

Given the wide variation in NA ancestry among Hispanic women, we investigated whether the associations with meat/fish variables differed by tertiles of NA ancestry (Supplemental Table 1). We observed that the positive association between diets high in processed meats and BC risk was found only in Hispanic women with intermediate (T3 vs. T1 OR = 1.62; 95% 1.10–2.40) and high (T3 vs. T1 OR = 1.88; 95% 1.19–2.95) NA ancestry, but not among women within the low category (T3 vs. T1 OR = 0.97; 95% 0.66–1.45), suggesting a possible modifying effect of NA ancestry; however, tests for heterogeneity were not statistically significant. Similarly, we observed that the inverse association with poultry intake was restricted to women with intermediate NA ancestry, but again we found no

evidence of significant heterogeneity. Furthermore, interaction tests were not significant when modeling admixture continuously. In unstratified models that included admixture as a covariate, associations between processed meat (T3 vs. T1 OR = 1.45; 95% CI 1.15–1.82; data not shown) and poultry intake (T3 vs. T1 OR = 0.79; 95% CI 0.64–0.98; data not shown) and BC risk remained statistically significant; whereas associations between tuna intake and BC risk did not.

Meat/fish variables and BC risk according to ER status

When considering BC subtypes defined by ER status, among NHW women (Table 4) we observed that the positive association with tuna intake was limited to ER+ BC cases (T3 vs. T1 OR = 1.46; 95% CI 1.18–1.81). No significant associations were observed for women with ER– BC (heterogeneity p = 0.003). Among Hispanic women (Table 5), associations with processed meat intake were only statistically significant among ER+ BC (T3 vs. T1 OR = 1.45; 95% CI 1.16–1.81, heterogeneity p = 0.004) as were associations with poultry (T3 vs. T1 OR = 0.77; 95% CI 0.63–0.94, heterogeneity p = 0.04) and white meat intake (T3 vs. T1 OR = 0.74; 95% CI 0.60–0.91, heterogeneity p = 0.02). Further stratification by menopausal status was not performed due to small numbers.

Meta-analysis results

To address any possible residual heterogeneity across the two case-control studies that was not accounted for by variable harmonization, adjustment for study, and use of study- and race/ethnicity-specific exposure cut-points, we also combined study- and race/ethnicity-specific ORs via random/fixed effects models, for NHW and Hispanic women separately. Results varied by study to a greater extent among NHW, where all significant associations seemed restricted to the SFBCS study. Upon pooling results via random effects models, tuna intake was still positively associated with BC risk (T3 vs. T1 combined OR = 1.31; 95% CI 0.90–1.91; p trend = 0.014) (Table 6).

Less heterogeneity across the two case-control studies was observed among Hispanics. Processed meat intake was positively associated in both 4-CBCS and SFBS studies. Likewise, white meat intake was consistently associated with decreased BC risk in both studies, Consequently, in combined analyses both processed meats (T3 vs. T1 combined OR = 1.38; 95% CI 1.14–1.67) and white meats (T3 vs. T1 combined OR = 0.78; 95% CI 0.65–0.93) were positively and inversely associated with BC risk, respectively (Table 6). Tuna and poultry intake were no longer statistically significantly associated with BC risk in meta-analysis, although results for poultry are still suggestive of an inverse association (Table 6).

Meta-analyses stratified by ER status yielded similar findings as those obtained with pooled analyses. Tuna associations among NHW women were limited to ER+ cases, whereas processed meat and white meat associations with BC risk maintained statistical significance only among Hispanic ER+ cases (Supplemental Table 2). Similarly to results from pooled analyses, poultry and tuna were not associated with either ER+ nor ER– among Hispanic women.

Discussion

In this pooled case-control analysis, we found evidence that diets high in tuna intake may increase the risk of BC risk among both NHW and Hispanic women, whereas positive associations with diets high in processed meats and inverse associations with diets high in poultry and white meat were found among Hispanic women only. The associations among Hispanic women did not seem to be modified by NA ancestry. Our findings were similar when combining estimates via random/fixed models: tuna intake was positively associated with BC risk among NHW women only, whereas processed and white meat intake were associated with increased and decreased risk of BC, respectively, among Hispanic women. To our knowledge, this is one of the first investigations of meat/fish intake and BC risk in a large population of US Hispanics.

Previous investigations of fish intake and BC risk have produced inconclusive results. A meta-analysis that included 11 prospective studies concluded that fish intake was not associated with BC risk [31]. Furthermore, a 2013 prospective study conducted among US black women also failed to find an association [32], as did a more recent prospective study conducted in Japan, where fish makes up a relatively higher proportion of daily dietary consumption [33]. In contrast, a prospective study from Denmark reported that overall intake of fish was associated with higher incidence rates of BC independently of fish fat content or preparation methods [34]. Several case-control studies have investigated fish intake and BC risk with inconclusive results, some reporting no evidence of association [20, 35–37], evidence of inverse associations for fatty fish among both pre- and post-menopausal women in Korea [38] and post-menopausal women in the US [39], or evidence of a positive association [40].

In this study, although overall fish consumption was not associated with BC risk, we found a positive association with tuna intake. None of the previously mentioned studies reported findings for specific fish species, such as tuna. The health benefits of fish intake are often attributed to the consumption of omega 3 polyunsaturated fatty acids (n-3 PUFA), which may act in several pathways that inhibit tumor progression [41]. In the previously mentioned meta-analysis, Zheng *et al* reported a protective effect for marine n-3 PUFA in a dose-responsive manner [31]. Nevertheless, the benefits of PUFA intake may be outweighed by exposures to chemical contaminants such as persistent organic pollutants and metals, potentially found in fish, contingent on species, portion size, and frequency of consumption [42]. Certain metals such as mercury and cadmium may activate estrogen receptors in the absence of estradiol, and there is epidemiological support for an association between exposure to these metals and an increased risk of BC [43]. In terms of PUFA content, tuna ranks relatively low compared to other commonly consumed species [44], but may be responsible for a greater share of exposures to chemical pollutants [42].. In the US, tuna is frequently consumed in canned form, and different types of canned tuna contain varying amounts of mercury contamination [45]. In our study, the 4-CBCS FFQ captured tuna intake information in terms of various canned tuna and tuna salad, while the SFBCS FFQ asked about overall tuna intake, such as fresh, canned, or as part of a dish. Thus, we could not investigate associations with specific tuna products separately. Therefore, this issue deserves further investigation. We cannot discard the possibility that the association between tuna

intake and BC risk may be driven by chance, given the number of comparisons we made, or by residual confounding by factors unmeasured in our study.

Several studies investigated processed meat intake and BC risk by grouping food items such as hotdogs, bacon, sausages, and luncheon meats, with equivocal results. Among 10 prospective studies, 4 studies reported statistically significant positive associations with processed meats [20, 46–48], 1 a non-statistically significant positive association [49], and 5 studies reported no associations [32, 50–53]. A pooled analysis of 8 additional cohort studies reported no association with processed meats [18]. In addition, among 7 population-based case-control studies that considered processed meats separately from unprocessed red meat, 5 reported a positive association with processed meats [36, 54–57], and 2 reported non-statistically significant positive associations [39, 58]. Recently, a meta-analysis of all available prospective studies reported a positive association with processed meats and breast cancer risk [59]; however, we note that this study included overlapping studies, therefore the conclusions may not be fully representative of the available data. Among 3 hospital-based case-control studies, 2 reported non-statistically significant positive associations [60, 61], and 1 reported no associations with processed meats [62]. In our study, we found that processed meat intake was associated with elevated BC risk among Hispanic women only, with no evidence of heterogeneity by menopausal status. We don't have a clear explanation for the racial/ethnic difference in our results. Although we attempted to adjust for most well-known putative confounders, the presence of additional unmeasured or unknown confounding factors is a possibility, particularly factors that may be unique to Hispanic women. Another possibility is the presence of a threshold effect for processed meats. In our study, Hispanic women consumed significantly higher mean levels of processed meats than NHW women (14.2 g/day vs. 12.4 g/day among controls) during the reference year. However, once processed meat intake is nutrient density adjusted (gm/1000 kcal/day), the differences in consumption per 1000 kcal are not as large. Hispanic cases and controls in the SFBCS study had lower levels of nutrient density adjusted processed meat consumption compared to NHW women, while Hispanic cases and controls in the 4-CBCS had higher levels compared to NHW women.

Given that breast development occurs during adolescence, early life exposures might be more influential in determining future BC risk than exposures during midlife [63]; a study done within the Nurses' Health Study II cohort reported a positive association between early adulthood total red meat consumption and BC risk [64]. In a related study using the same cohort, an association was reported between BC risk in pre-menopausal women and total red meat consumption and total processed meats during high school [65]. Acculturation after migration to the US may contribute to a net increase in intake of unhealthy food sources among Mexican women [66]. Thus, it is plausible that Hispanic adolescent exposures to higher levels of processed meats may explain our results. Another possibility is that the differences in the observed associations for processed meats may be due to ethnic differences in genetic susceptibility to exposure to meat-related carcinogens. Two studies, among Danish and Chinese populations, found evidence of interaction between red and smoked meat intake, respectively, and the carcinogen metabolism enzymes NAT1 and NAT2 [20, 21]. In our analyses, adjustment and stratification by NA ancestry categories did not change results dramatically, suggesting that associations with processed meats, or other risk

factors captured by this exposure, are similar across Hispanic women, regardless of possible differences at the genetic level. Further research is necessary to clarify the nature of the association between processed meats and BC risk among Hispanics.

It is also unclear why poultry and white meat were protective only among Hispanic women. Although the poultry association did not retain statistical significance when combining results via meta-analysis for all women combined, there was still evidence of a significant association in stratified analyses by menopausal status. Evidence for poultry and white meat intake is inconclusive, with many investigations of poultry yielding null results [20, 37, 61, 67], with a few finding positive associations with BC risk [40, 58]. Like processed meats, there could be differences in the timing of exposure (e.g. earlier in adolescence versus late) [65]. We cannot discard residual confounding, as high intake of white meats may indicate overall healthier eating patterns [68]. White meat and processed meat intake were negatively correlated, but the correlation coefficients were very small, and did not differ by race/ ethnicity.

To our knowledge, this is the first study to examine the association between meat/fish intake and BC risk among Hispanic women in comparison with NHWs. Our study has many strengths, such as the inclusion a large number of Hispanic women in addition to NHWs, with a large proportion of women contributing data on meat intake and ER and PR status. In addition, we were able to consider global genetic ancestry in an effort to control for the known genetic heterogeneity among Hispanics. Limitations include the harmonized food intake data from two different FFQs, which could introduce artificial variability in consumption levels. We attempted to address this by creating tertiles based on study-specific cutoff levels, and by adjusting meat/fish intake levels by energy intake. We also conducted meta-analysis of study- and race/ethnicity-specific odds ratios in order to corroborate findings using these harmonized categorical variables and account further for possible inter-study heterogeneity. Another limitation of our study was the inability to harmonize cooking methods information, which would have allowed estimation of mutagen consumption and also closer investigation of the tuna intake associations. We also recognize that participation rates were lower in 4-CBCS compared to SFBCS, adding the possibility of selection bias and biased exposure reports. All our analyses adjusted for study center, so much of the variability introduced by these factors may have been attenuated.

In summary, we report that diets high in tuna fish may increase risk of BC among NHW and possibly also among Hispanic women. Moreover, we observed that diets high in processed meats may increase risk of BC risk among Hispanic women, albeit not comparable evidence was observed among NHWs. Further research is needed to understand the possible reason for the ethnic differences in associations with processed meat intake and the role of processed meats in BC formation among Latinas.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Demographic characteristics of cases and controls, stratified by race/ethnicity.

N = 8242[a]	Non-Hispanic White (NHW)			Hispanic			NHW vs. Hispanic controls
	Controls (N=2,218)	Cases (N=1,982)	p value	Controls (N=2,265)	Cases (N=1,777)	p value	p value
Age (Years)							
Mean (SD)	56.9 (12.2)	56.5 (11.4)	0.2876	54.2 (11.5)	53.7 (11.3)	0.1569	< 0.001
Menopausal Status (%)[b]							
Pre-menopausal	663 (29.9)	631 (31.8)	0.202	787 (34.7)	669 (37.6)	0.058	< 0.001
Post-menopausal	1494 (67.4)	1305 (65.8)		1358 (60.0)	1017 (57.2)		
Family History (%)[c]							
No	1825 (82.3)	1505 (75.9)	< 0.001	1978 (87.3)	1472 (82.8)	< 0.001	< 0.001
Yes	321 (14.5)	430 (21.7)		224 (9.9)	266 (15.0)		
Education (%)[d]							
Less than high school grad	112 (5.0)	93 (4.7)	0.647	972 (42.9)	628 (35.3)	< 0.001	< 0.001
High school grad/GED	467 (21.1)	400 (20.2)		495 (21.9)	417 (23.5)		
Post high school education	1637 (73.8)	1487 (75.0)		713 (31.5)	696 (39.2)		
Alcohol Consumption (%)[e]							
None	1080 (48.7)	866 (43.7)	0.007	1540 (68.0)	1143 (64.3)	0.013	< 0.001
Low (<5gm/day)	542 (24.4)	514 (25.9)		429 (18.9)	347 (19.5)		
Moderate (5 to <10gm/day)	214 (9.6)	220 (11.1)		117 (5.2)	102 (5.7)		
High (>=10gm/day)	353 (15.9)	363 (18.3)		158 (7.0)	169 (9.5)		
Parity (%)[f]							
Nulliparous	353 (15.9)	366 (18.5)	< 0.001	159 (7.0)	199 (11.2)	< 0.001	< 0.001
1 – 2 births	917 (41.3)	907 (45.8)		683 (30.2)	690 (38.8)		
3 – 4 births	727 (32.8)	581 (29.3)		879 (38.8)	610 (34.3)		
5+ births	217 (9.8)	126 (6.4)		542 (23.9)	276 (15.5)		
Age at First Birth (%)[g]							
Nulliparous	353 (15.9)	366 (18.5)	0.112	159 (7.0)	199 (11.2)	< 0.001	< 0.001
< 26	273 (12.3)	242 (12.2)		615 (27.2)	384 (21.6)		
26 – 30	805 (36.3)	655 (33.0)		827 (36.5)	655 (36.9)		

N = 8242[a]	Non-Hispanic White (NHW)			Hispanic			NHW vs. Hispanic controls
	Controls (N=2,218)	Cases (N=1,982)	p value	Controls (N=2,265)	Cases (N=1,777)	p value	p value
31 – 35	508 (22.9)	457 (23.1)		431 (19.0)	320 (18.0)		
> 35	275 (12.4)	258 (13.0)		213 (9.4)	216 (12.2)		
Physical Activity (%)							
Low	806 (36.3)	780 (39.4)	0.109	1344 (59.3)	1070 (60.2)	0.249	<0.001
Medium	611 (27.5)	537 (27.1)		531 (23.4)	386 (21.7)		
High	561 (25.3)	485 (24.5)		299 (13.2)	261 (14.7)		
Highest	240 (10.8)	180 (9.1)		91 (4.0)	60 (3.4)		
Oral Contraceptive (%)[i]							
Ever	729 (32.9)	585 (29.5)	0.084	978 (43.2)	696 (39.2)	0.051	<0.001
Never	1468 (66.2)	1323 (66.8)		1256 (55.5)	1015 (57.1)		
Hormone Replacement Therapy (%)[j]							
Ever	621 (28.0)	542 (27.3)	0.765	1204 (53.2)	907 (51.0)	0.765	<0.001
Never	1256 (56.6)	1120 (56.5)		852 (37.6)	655 (36.9)		
BMI[h]							
Mean (SD)	27.2 (6.2)	27.0 (6.0)	0.2284	30.0 (6.0)	29.1 (6.0)	<0.001	<0.001
Caloric Intake - Kcal/day							
Mean (SD) SFBCS	1943.9 (776.6)	1913.6 (765.7)	0.4906	2221.2 (904.4)	2257.0 (904.6)	0.3227	<0.001
Mean (SD) 4-CBCS	2091.8 (885.8)	2181.8 (891.2)	0.0059	2532.3 (1151.2)	2588.8 (1141.2)	0.3443	<0.001
Fiber Intake - gm/day							
Mean (SD) SFBCS	18.5 (10.2)	17.6 (8.5)	0.1161	28.9 (17.2)	25.4 (13.8)	<0.001	<0.001
Mean (SD) 4-CBCS	24.1 (11.9)	24.7 (11.7)	0.1747	31.2 (16.4)	31.0 (15.1)	0.8534	<0.001
Carbohydrates Intake - gm/day							
Mean (SD) SFBCS	233.5 (100.4)	221.3 (89.8)	0.025	290.9 (128.0)	283.9 (118.2)	0.1538	<0.001
Mean (SD) 4-CBCS	259.2 (113.5)	272.8 (115.0)	0.0012	316.4 (148.0)	328.3 (142.7)	0.1165	<0.001
Fats Intake - gm/day							
Mean (SD) SFBCS	72.0 (36.9)	72.5 (38.0)	0.8	71.9 (34.7)	78.9 (38.8)	<0.001	0.9378
Mean (SD) 4-CBCS	83.1 (44.1)	85.7 (43.8)	0.105	102.4 (54.1)	102.8 (54.6)	0.8756	<0.001
Protein Intake - gm/day							
Mean (SD) SFBCS	81.8 (33.4)	83.0 (35.0)	0.5563	98.5 (41.8)	97.2 (41.8)	0.4578	<0.001

N = 8242[a]	Non-Hispanic White (NHW)			Hispanic			NHW vs. Hispanic controls
	Controls (N=2,218)	Cases (N=1,982)	p value	Controls (N=2,265)	Cases (N=1,777)	p value	p value
Mean (SD) 4-CBCS	82.5 (35.7)	84.8 (35.3)	0.0842	96.5 (44.6)	97.9 (45.7)	0.5496	< 0.001
Red Meat Intake - gm/kcal/day							
Mean (SD) SFBCS	17.3 (15.9)	20.0 (17.0)	0.004	17.7 (15.9)	19.2 (16.4)	0.0193	0.5906
Mean (SD) 4-CBCS	36.5 (21.3)	35.6 (21.1)	0.2694	38.0 (21.6)	38.2 (21.5)	0.8732	0.0964
Processed Meat Intake - gm/kcal/day							
Mean (SD) SFBCS	6.8 (8.9)	8.1 (9.6)	0.0085	5.8 (8.2)	7.5 (9.2)	< 0.001	0.0215
Mean (SD) 4-CBCS	5.4 (6.0)	5.1 (5.6)	0.1653	6.1 (7.1)	6.3 (6.2)	0.601	0.015
Poultry Intake - gm/kcal/day							
Mean (SD) SFBCS	26.9 (21.6)	27.7 (20.8)	0.5308	25.8 (19.7)	24.3 (18.7)	0.565	0.2423
Mean (SD) 4-CBCS	19.9 (16.3)	19.5 (15.8)	0.4823	17.4 (16.4)	16.7 (14.5)	0.3415	0.0005
Fish Intake - gm/kcal/day							
Mean (SD) SFBCS	16.9 (15.9)	19.5 (18.1)	0.0068	13.5 (15.4)	14.8 (16.8)	0.0459	< 0.001
Mean (SD) 4-CBCS	8.8 (10.6)	8.9 (10.5)	0.8882	6.6 (9.2)	6.3 (8.8)	0.5257	< 0.001
Tuna Intake - gm/kcal/day							
Mean (SD) SFBCS	7.7 (9.3)	9.7 (11.9)	0.001	6.3 (10.1)	7.3 (11.1)	0.0271	0.003
Mean (SD) 4-CBCS	4.0 (6.1)	4.3 (7.0)	0.1694	3.8 (6.8)	3.6 (6.0)	0.5407	0.5408
White Meat Intake - gm/kcal/day							
Mean (SD) SFBCS	43.8 (29.3)	47.2 (27.8)	0.038	39.3 (26.4)	39.1 (26.7)	0.861	0.0005
Mean (SD) 4-CBCS	28.7 (21.5)	28.3 (20.4)	0.64	24.0 (20.3)	23.0 (18.4)	0.292	< 0.001

[a] Excludes subjects with extremes caloric intake values (<600 kcal/day or >6000 kcal/day). Primary, invasive BC cases only. Where applicable, study specific statistics are presented: 4 Corner Breast Cancer Study (4-CBCS), San Francisco Bay Area Breast Cancer Study (SFBCS).

[b] 318 observations missing menopause status, percentages do not add to 100

[c] 221 observations missing family history, percentages do not add to 100

[d] 125 observations missing education, percentages do not add to 100

[e] 85 observations missing alcohol consumption, percentages do not add to 100

[f] 10 observations missing parity, percentages do not add to 100

[g] 31 observations missing age at first birth, percentages do not add to 100

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[h]50 observations missing BMI

[i]192 observations missing oral contraceptive use, percentages do not add to 100

[j]1085 observations missing hormone replace therapy (1032 pre-menopausal, 50 post-menopausal), percentages do not add to 100.

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Table 2

Meat/fish intake and breast cancer risk among Non-Hispanic White women, by menopausal status.

Energy Adjusted grams/day[c]	All Non-Hispanic White women			Pre-menopausal			Post-menopausal			Heterogeneity p value[b]
	Co/Ca	OR[a] (95% CI)	p value	Co/Ca	OR[a] (95% CI)	p value	Co/Ca	OR[a] (95% CI)	p value	
Red Meat (Non-Processed)										
T1: 15.9/3.9	690|623	1.0 REF		202|181	1.0 REF		488|442	1.0 REF		0.4843
T2: 34.7/13.7	677|591	0.97 (0.82–1.14)	0.69	211|207	1.07 (0.80–1.44)	0.635	466|384	0.89 (0.73–1.09)	0.254	
T3: 55.7/28.4	685|648	1.04 (0.88–1.23)	0.631	212|202	1.08 (0.79–1.48)	0.618	473|446	0.99 (0.81–1.22)	0.952	
Trend	N=3914		0.617	N=1215		0.623	N=2699		0.98	
Processed Meat										
T1: 0.8/0.0	676|578	1.0 REF		207|175	1.0 REF		469|403	1.0 REF		0.5577
T2: 3.6/3.8	687|624	1.05 (0.89–1.23)	0.593	235|224	1.14 (0.85–1.51)	0.387	452|400	1.01 (0.83–1.23)	0.951	
T3: 9.5/12.2	689|660	1.10 (0.93–1.31)	0.25	183|191	1.29 (0.94–1.78)	0.109	506|469	1.03 (0.85–1.27)	0.741	
Trend	N=3914		0.249	N=1215		0.109	N=2699		0.737	
Poultry										
T1: 6.4/7.9	694|608	1.0 REF		153|160	1.0 REF		541|448	1.0 REF		0.0816
T2: 16.2/21.0	676|655	1.09 (0.93–1.28)	0.278	247|219	0.85 (0.63–1.15)	0.29	429|436	1.21 (1.00–1.46)	0.049	
T3: 32.0/47.0	682|599	0.99 (0.84–1.16)	0.904	225|211	0.89 (0.66–1.20)	0.441	457|388	1.00 (0.83–1.21)	0.988	
Trend	N=3914		0.896	N=1215		0.496	N=2699		0.926	
Fish										
T1: 1.39/4.1	679|566	1.0 REF		228|204	1.0 REF		451|362	1.0 REF		0.3551
T2: 5.8/12.3	679|661	1.17 (1.00–1.37)	0.05	216|198	1.04 (0.79–1.37)	0.801	463|463	1.23 (1.01–1.49)	0.038	
T3: 14.9/30.2	694|635	1.09 (0.93–1.29)	0.289	181|188	1.16 (0.86–1.55)	0.323	513|447	1.06 (0.87–1.29)	0.572	
Trend	N=3914		0.299	N=1215		0.331	N=2699		0.638	
Tuna										
T1: 0.0/0.0	399|322	1.0 REF		129|105	1.0 REF		270|217	1.0 REF		0.8787
T2: 1.4/4.6	821|705	1.06 (0.88–1.27)	0.546	263|235	1.07 (0.77–1.48)	0.687	558|470	1.03 (0.83–1.29)	0.78	
T3: 6.1/11.1	832|835	1.25 (1.05–1.50)	0.015	233|250	1.33 (0.96–1.84)	0.083	599|585	1.20 (0.97–1.49)	0.099	
Trend	N=3914		0.006	N=1215		0.053	N=2699		0.055	
White Meat										
T1: 11.2/18.5	690|617	1.0 REF		178|177	1.0 REF		512|440	1.0 REF		0.6557

Energy Adjusted grams/day[c]	All Non-Hispanic White women			Pre-menopausal			Post-menopausal			Heterogeneity p value[b]
	Co/Ca	OR[a] (95% CI)	p value	Co/Ca	OR[a] (95% CI)	p value	Co/Ca	OR[a] (95% CI)	p value	
T2: 23.7/37.6	684|586	0.95 (0.81–1.12)	0.554	238|198	0.87 (0.65–1.16)	0.352	446|388	0.99 (0.82–1.20)	0.922	
T3: 45.2/71.7	678|659	1.07 (0.92–1.26)	0.374	209|215	1.03 (0.77–1.39)	0.831	469|444	1.08 (0.89–1.30)	0.457	
Trend	N=3914		0.366	N=1215		0.788	N=2699		0.457	

Co/Ca: controls/cases; 1.0REF: reference

[a] Adjusted for age, study, family history, menopausal status (in combined analyses), parity/age at first birth, BMI, education, alcohol intake, physical activity, calorie intake, fiber intake, fat intake.

[b] Test of heterogeneity by menopausal status. Meat/fish modeled categorically - 2df

[c] Tertile: study specific (4 Corner Breast Cancer Study/San Francisco Bay Area Breast Cancer Study) median intake among Non-Hispanic White controls.

Table 3

Meat/fish intake and breast cancer risk among Hispanic women, by menopausal status.

Energy Adjusted grams/day[c]	All Hispanic women			Pre-menopausal			Post-menopausal			Heterogeneity p value[b]
	Co/Ca	OR[a] (95% CI)	p value	Co/Ca	OR[a] (95% CI)	p value	Co/Ca	OR[a] (95% CI)	p value	
Red Meat (non-processed)										
T1: 17.8/4.3	643|487	1.0 REF		204|166	1.0 REF		439|321	1.0 REF		0.9621
T2: 35.7/14.0	656|534	1.01 (0.85–1.20)	0.898	254|218	0.98 (0.73–1.32)	0.897	402|316	1.02 (0.82–1.26)	0.855	
T3: 56.0/28.9	664|572	1.01 (0.85–1.21)	0.894	270|253	0.99 (0.73–1.35)	0.967	394|319	1.01 (0.81–1.26)	0.949	
Trend	N=3556		0.896	N=1365		0.978	N=2191		0.948	
Processed Meat										
T1: 1.1/0.0	655|410	1.0 REF		218|141	1.0 REF		437|269	1.0 REF		0.3914
T2: 4.2/3.2	647|550	1.32 (1.10–1.57)	0.002	272|234	1.38 (1.03–1.87)	0.033	375|316	1.34 (1.07–1.68)	0.01	
T3: 10.4/10.8	661|633	1.42 (1.18–1.71)	<0.001	238|262	1.69 (1.22–2.33)	0.001	423|371	1.34 (1.06–1.68)	0.014	
Trend	N=3556		<0.001	N=1365		0.002	N=2191		0.017	
Poultry										
T1: 4.9/8.2	640|532	1.0 REF		194|181	1.0 REF		446|351	1.0 REF		0.509
T2: 12.9/21.5	654|568	0.99 (0.84–1.16)	0.875	253|225	0.84 (0.63–1.12)	0.245	401|343	1.06 (0.86–1.30)	0.584	
T3: 28.1/43.7	669|493	0.80 (0.67–0.95)	0.011	281|231	0.72 (0.54–0.96)	0.027	388|262	0.82 (0.66–1.02)	0.079	
Trend	N=3556		0.011	N=1365		0.026	N=2191		0.099	
Fish										
T1: 0.2/0.0	626|480	1.0 REF		225|197	1.0 REF		401|283	1.0 REF		0.205
T2: 3.9/8.8	654|540	1.05 (0.89–1.25)	0.547	275|217	0.93 (0.70–1.23)	0.602	379|323	1.17 (0.94–1.45)	0.165	
T3: 11.6/24.2	683|573	1.06 (0.89–1.25)	0.532	228|223	1.09 (0.82–1.46)	0.539	455|350	1.05 (0.84–1.30)	0.686	
Trend	N=3556		0.54	N=1365		0.521	N=2191		0.736	
Tuna										
T1: 0.0/0.0	630|418	1.0 REF		215|165	1.0 REF		415|253	1.0 REF		0.3328
T2: 1.3/4.1	648|579	1.29 (1.08–1.53)	0.005	266|232	1.03 (0.77–1.38)	0.83	382|347	1.49 (1.19–1.86)	0.001	
T3: 6.0/11.1	685|596	1.21 (1.02–1.44)	0.03	247|240	1.08 (0.80–1.44)	0.62	438|356	1.29 (1.04–1.61)	0.023	
Trend	N=3556		0.045	N=1365		0.615	N=2191		0.039	
White Meat										
T1: 7.5/14.9	633|537	1.0 REF		207|188	1.0 REF		426|349	1.0 REF		0.88

Energy Adjusted grams/day[c]	All Hispanic women			Pre-menopausal			Post-menopausal			Heterogeneity p value[b]
	Co/Ca	OR[a] (95% CI)	p value	Co/Ca	OR[a] (95% CI)	p value	Co/Ca	OR[a] (95% CI)	p value	
T2: 19.0/33.7	655|546	0.93 (0.79–1.10)	0.403	248|221	0.87 (0.65–1.16)	0.334	407|325	0.96 (0.78–1.18)	0.675	
T3: 37.6/63.5	675|510	0.80 (0.67–0.95)	0.01	273|228	0.76 (0.57–1.01)	0.061	402|282	0.81 (0.65–1.00)	0.052	
Trend	N=3556		0.01	N=1365		0.06	N=2191		0.055	

Co/Ca: controls/cases; 1.0REF: reference

[a] Adjusted for age, study, family history, menopausal status (in combined analyses), parity/age at first birth, BMI, education, alcohol intake, physical activity, calorie intake, fiber intake, fat intake.

[b] Test of heterogeneity by menopausal status. Meat/fish modeled categorically - 2df

[c] Tertile: study specific (4 Corner Breast Cancer Study/San Francisco Bay Area Breast Cancer Study) median intake among Hispanic controls.

Table 4

Meat/fish intake and breast cancer risk by tumor estrogen receptor (ER) status among Non-Hispanic White women.

Energy Adjusted grams/day[b]	Controls	ER+	ER−	ER+ vs. Control OR[a] (95% CI)	p value	ER− vs. control OR[a] (95% CI)	p value	Heterogeneity p value[c]
Red Meat (Non-Processed)								
T1: 15.9/3.9	690	385	84	1.0REF		1.0REF		p = 0.95
T2: 34.7/13.7	677	365	76	0.95 (0.79–1.15)	0.6061	0.77 (0.54–1.08)	0.1252	
T3: 55.7/28.4	685	396	102	1.01 (0.83–1.22)	0.9493	0.93 (0.67–1.31)	0.6974	
Trend					0.9359		0.7739	
Processed Meat								
T1: 0.8/0.0	676	341	76	1.0REF		1.0REF		p = 0.33
T2: 3.6/3.8	687	389	86	1.10 (0.91–1.33)	0.3059	0.96 (0.68–1.34)	0.8	
T3: 9.5/12.2	689	416	100	1.16 (0.95–1.41)	0.1351	1.06 (0.75–1.50)	0.7423	
Trend					0.1384		0.7128	
Poultry								
T1: 6.4/7.9	694	380	73	1.0REF		1.0REF		p = 0.7
T2: 16.2/21.0	676	395	96	1.06 (0.88–1.27)	0.556	1.20 (0.86–1.67)	0.2887	
T3: 32.0/47.0	682	371	93	0.98 (0.81–1.18)	0.8235	1.14 (0.82–1.60)	0.4347	
Trend					0.8192		0.4575	
Fish								
T1: 1.39/4.1	679	332	93	1.0REF		1.0REF		p = 0.26
T2: 5.8/12.3	679	420	92	1.25 (1.04–1.51)	0.0154	1.05 (0.77–1.44)	0.7634	
T3: 14.9/30.2	694	394	77	1.15 (0.95–1.39)	0.1444	0.92 (0.66–1.28)	0.6123	
Trend					0.157		0.6201	
Tuna								
T1: 0.0/0.0	399	173	57	1.0REF		1.0REF		p = 0.003
T2: 1.4/4.6	821	454	94	1.29 (1.04–1.61)	0.0199	0.80 (0.56–1.15)	0.2247	
T3: 6.1/11.1	832	519	111	1.46 (1.18–1.81)	0.0005	0.98 (0.69–1.39)	0.9198	
Trend					0.0007		0.819	
White Meat								

Energy Adjusted grams/day[b]	Controls	ER+	ER−	ER+ vs. Control		ER- vs. control		Heterogeneity p value[c]
				OR[a] (95% CI)	p value	OR[a] (95% CI)	p value	
T1: 11.2/18.5	690	384	76	1.0REF		1.0REF		p = 0.41
T2: 23.7/37.6	684	344	93	0.90 (0.75–1.09)	0.2835	1.17 (0.84–1.62)	0.3546	
T3: 45.2/71.7	678	418	93	1.10 (0.91–1.31)	0.3288	1.20 (0.86–1.68)	0.273	
Trend					0.3145		0.2845	

1.0REF : reference

[a] Adjusted for age, center, family history, menopausal status, parity/age at first birth, BMI, education, alcohol intake, physical activity, calorie intake, fiber intake, fat intake.

[b] Tertile: study specific (4 Corner Breast Cancer Study/San Francisco Bay Area Breast Cancer Study) median intake among Non-Hispanic White controls.

[c] Heterogeneity test by tumor estrogen receptor status.

Table 5

Meat/fish intake and breast cancer risk by tumor estrogen receptor (ER) status among Hispanic women.

Energy Adjusted grams/day[b]	Controls	ER +	ER–	ER+ vs. Control OR[a] (95% CI)	p value	ER– vs. control OR[a] (95% CI)	p value	Heterogeneity p value[c]
Red Meat (non-processed)								p = 0.22
T1: 17.8/4.3	643	292	89	1.0 REF		1.0 REF		
T2: 35.7/14.0	656	307	103	0.97 (0.79–1.18)	0.7418	1.02 (0.74–1.40)	0.9064	
T3: 56.0/28.9	664	317	133	0.92 (0.74–1.13)	0.4156	1.23 (0.89–1.69)	0.2068	
Trend					0.4127		0.1824	
Processed Meat								p = 0.004
T1: 1.1/0.0	655	228	88	1.0 REF		1.0 REF		
T2: 4.2/3.2	647	316	109	1.38 (1.11–1.70)	0.0032	1.17 (0.85–1.61)	0.3292	
T3: 10.4/10.8	661	372	128	1.45 (1.16–1.81)	0.0009	1.32 (0.95–1.83)	0.0993	
Trend					0.0013		0.0962	
Poultry								p = 0.04
T1: 4.9/8.2	640	318	104	1.0 REF		1.0 REF		
T2: 12.9/21.5	654	317	116	0.93 (0.76–1.13)	0.4503	1.02 (0.76–1.37)	0.8922	
T3: 28.1/43.7	669	281	105	0.77 (0.63–0.94)	0.0116	0.86 (0.63–1.17)	0.3309	
Trend					0.0118		0.3266	
Fish								p = 0.94
T1: 0.2/0.0	626	272	107	1.0 REF		1.0 REF		
T2: 3.9/8.8	654	322	101	1.09 (0.89–1.34)	0.3962	0.90 (0.66–1.21)	0.4763	
T3: 11.6/24.2	683	322	117	0.99 (0.81–1.22)	0.9403	1.04 (0.77–1.41)	0.7817	
Trend					0.9026		0.7668	
Tuna								p = 0.26
T1: 0.0/0.0	630	244	84	1.0 REF		1.0 REF		
T2: 1.3/4.1	648	333	124	1.28 (1.04–1.58)	0.0191	1.43 (1.05–1.95)	0.0234	
T3: 6.0/11.1	685	339	117	1.17 (0.95–1.44)	0.1386	1.24 (0.91–1.70)	0.1745	
Trend					0.1788		0.2213	
White Meat								p = 0.02

Energy Adjusted grams/day[b]	Controls	ER +	ER−	ER+ vs. Control		ER− vs. control		Heterogeneity p value[c]
				OR[a] (95% CI)	p value	OR[a] (95% CI)	p value	
T1: 7.5/14.9	633	313	107	1.0 REF		1.0 REF		
T2: 19.0/33.7	655	322	101	0.93 (0.77–1.14)	0.4877	0.89 (0.66–1.20)	0.4281	
T3: 37.6/63.5	675	281	117	0.74 (0.60–0.91)	0.0041	0.95 (0.71–1.29)	0.7572	
Trend				0.0041		0.7731		

1.0REF : reference

[a] Adjusted for age, center, family history, menopausal status, parity/age at first birth, BMI, education, alcohol intake, physical activity, calorie intake, fiber intake, fat intake.

[b] Tertile: study specific (4 Corner Breast Cancer Study/San Francisco Bay Area Breast Cancer Study) median intake among Hispanic controls.

[c] Heterogeneity test by tumor estrogen receptor status.

Table 6

Multivariate-adjusted[a] meta odds ratios (95% CI) of breast cancer from 4-CBCS and SFBCS, by race/ethnicity

Exposure	Tertile 1 REF	Tertile 2 OR[a]	Tertile 2 (95% CI)	Tertile 3 OR[a]	Tertile 3 (95% CI)	Trend p value	Cochran Q[b]	I²[b] (%)	Meta-Analysis Model[c]
Non-Hispanic White Women									
Red meat	1.0 REF	1.03	(0.70–1.51)	1.14	(0.69–1.87)	0.55	0.0088	85	random
Processed meat	1.0 REF	1.04	(0.88–1.22)	1.21	(0.72–2.02)	0.514	0.0072	86	random
Poultry	1.0 REF	1.21	(0.66–2.25)	1.03	(0.77–1.38)	0.858	0.103	62	random
Fish	1.0 REF	1.22	(0.89–1.68)	1.19	(0.76–1.85)	0.576	0.0155	83	random
Tuna	1.0 REF	1.04	(0.86–1.25)	1.31	(0.90–1.91)	0.014	0.0547	73	random
White meat	1.0 REF	1.02	(0.68–1.53)	1.17	(0.75–1.85)	0.424	0.0114	84	random
Non-Hispanic White Women (pre-menopausal)									
Red meat	1.0 REF	1.13	(0.72–1.75)	1.28	(0.54–3.00)	0.5302	0.0183	82	random
Processed meat	1.0 REF	1.12	(0.83–1.50)	1.37	(0.85–2.22)	0.0856	0.1846	43	random
Poultry	1.0 REF	1.07	(0.34–3.40)	1.01	(0.48–2.11)	0.8108	0.0395	76	random
Fish	1.0 REF	1.06	(0.80–1.40)	1.32	(0.72–2.44)	0.2672	0.0687	70	random
Tuna	1.0 REF	1.07	(0.75–1.50)	1.38	(0.93–2.03)	0.019	0.2597	21	random
White meat	1.0 REF	0.87	(0.65–1.17)	1.18	(0.58–2.39)	0.6176	0.0418	76	random
Non-Hispanic White Women (post-menopausal)									
Red meat	1.0 REF	0.93	(0.65–1.34)	1.05	(0.71–1.56)	0.737	0.0815	67	random
Processed meat	1.0 REF	1	(0.82–1.22)	1.12	(0.65–1.93)	0.7374	0.016	83	random
Poultry	1.0 REF	1.29	(0.82–2.03)	1	(0.82–1.21)	0.7896	0.411	0	random
Fish	1.0 REF	1.3	(0.84–2.01)	1.14	(0.71–1.82)	0.8778	0.0356	77	random
Tuna	1.0 REF	1	(0.80–1.26)	1.24	(0.84–1.84)	0.1368	0.0951	64	random
White meat	1.0 REF	1.08	(0.63–1.84)	1.14	(0.76–1.70)	0.4286	0.0586	72	random
Hispanic Women									
Red meat	1.0 REF	1.03	(0.87–1.23)	1.03	(0.86–1.24)	0.8434	0.6781	0	fixed
Processed meat	1.0 REF	1.35	(1.13–1.62)	1.38	(1.14–1.67)	0.0072	0.4435	0	fixed
Poultry	1.0 REF	0.98	(0.83–1.17)	0.81	(0.59–1.11)	0.0702	0.0776	68	random

Exposure	Tertile 1		Tertile 2		Tertile 3		Trend p value	Cochran Q[b]	I²[b] (%)	Meta-Analysis Model[c]
	REF	OR[a]	(95% CI)	OR[a]	(95% CI)				
Fish	1.0 REF	1.04	(0.87–1.23)	1.02	(0.86–1.22)	0.7194	0.6538	0	fixed
Tuna	1.0 REF	1.29	(1.08–1.54)	1.18	(0.99–1.41)	0.2354	0.919	0	fixed
White meat	1.0 REF	0.93	(0.79–1.1)	0.78	(0.65–0.93)	0.0036	0.5996	0	fixed
Hispanic Women (pre-menopausal)									
Red meat	1.0 REF	1	(0.74–1.35)	1.02	(0.74–1.4)	0.9982	0.5261	0	fixed
Processed meat	1.0 REF	1.41	(0.86–2.3)	1.79	(0.92–3.51)	0.1136	0.05	74	random
Poultry	1.0 REF	0.85	(0.63–1.14)	0.7	(0.52–0.95)	0.0156	0.2873	12	fixed
Fish	1.0 REF	0.89	(0.67–1.19)	1.08	(0.8–1.45)	0.5332	0.5237	0	fixed
Tuna	1.0 REF	1.01	(0.75–1.36)	1.11	(0.82–1.49)	0.4094	0.58	0	fixed
White meat	1.0 REF	0.88	(0.66–1.18)	0.75	(0.56–1.01)	0.0676	0.9347	0	fixed
Hispanic Women (post-menopausal)									
Red meat	1.0 REF	1.05	(0.84–1.31)	1.01	(0.81–1.27)	0.9386	0.9887	0	fixed
Processed meat	1.0 REF	1.41	(1.12–1.77)	1.29	(1.02–1.63)	0.1298	0.6211	0	fixed
Poultry	1.0 REF	1.06	(0.86–1.31)	0.82	(0.65–1.02)	0.036	0.2322	30	fixed
Fish	1.0 REF	1.15	(0.92–1.44)	1.01	(0.81–1.26)	0.9802	0.2976	8	fixed
Tuna	1.0 REF	1.48	(1.18–1.87)	1.24	(0.99–1.55)	0.3276	0.5659	0	fixed
White meat	1.0 REF	0.95	(0.77–1.17)	0.79	(0.63–0.98)	0.0258	0.6045	0	fixed

1.0REF : reference

[a] Adjusted for age, study, family history, menopausal status (in combined analyses), parity/age at first birth, BMI, education, alcohol intake, physical activity, calorie intake, fiber intake, fat intake.

[b] Study heterogeneity tests for meta odds ratios comparing Tertile 3 vs. Tertile 1 - Cochran Q p values, I² percent.

[c] Random effects model used in all analysis performed on Non-Hispanic White Women. Fixed effects model used in analysis of Hispanic women, unless Cochran Q < 0.05 or I² > 50%