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Modifying Effects of IL-6 Polymorphisms on Body Size–Associated Breast Cancer Risk

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Abstract

Objective—The association between obesity and breast cancer risk is complex. We examined whether the association between body size and breast cancer risk is modified by interleukin-6 (*IL6*) genotype.

Methods and Procedures—Five polymorphisms in the IL-6 gene (rs1800797/-596A>G, rs1800796/-572G>C, rs1800795/-174G>C, rs2069832/IVS2G>A, and rs2069849 exon 5 C>T) were studied. We investigated *IL6* genotypes and haplotypes with indicators of body size among non-Hispanic white (NHW) and Hispanic/American Indian (AI) breast cancer cases and controls living in the Southwestern United States.

Results—We observed lower mean levels of BMI among NHW women who carried one or two copies of the GGCAC haplotype (in order: rs1800797, rs1800796, rs1800795, rs2069832, and rs2069849; *P* trend 0.02). This haplotype, with an estimated frequency of 43% in NHW study controls, was considerably less common in Hispanic/AI controls (19%). We did not detect significant interactions between *IL6* genotypes or haplotypes and BMI categorized as low/normal (<25), overweight (25 to <30), or obese (≥30) and breast cancer risk in either NHW or Hispanic/AI women. However, we detected consistent and significant interactions between waist-to-hip ratio (WHR) and *IL6* rs1800795/-174 G>C genotype for breast cancer risk. These associations were restricted to postmenopausal NHW women. Among women without recent hormone exposure, those with a WHR >0.9 and the rs1800795 GG genotype had a greater than threefold increased risk of breast cancer (odds ratios (ORs) 3.22, 95% confidence intervals (CIs) 1.27, 817) when compared with women with a WHR <0.8 and the rs1800795 GG genotype (*P* interaction 0.01).

Discussion—These data suggest that IL-6 genotypes may influence breast cancer risk in conjunction with central adiposity.

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DISCLOSURE
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INTRODUCTION

The association between body size and breast cancer risk has been shown to vary by menopausal status, with obesity reducing the risk of breast cancer among premenopausal women and increasing the risk among postmenopausal women (1). Some studies have also shown that postmenopausal women not receiving hormone replacement therapy (HRT) appear to be at greater risk for obesity-related breast cancer than postmenopausal women receiving HRT (2). Weight cycling and age at onset of obesity may further define the relationship between body size and breast cancer risk (3). We have added to this complex picture of breast cancer risk associated with body size through our observation that unlike non-Hispanic white (NHW) women, Hispanic and American Indian (AI) women are at reduced risk of breast cancer throughout their lives if they are obese (4). The biological basis for the pattern of breast cancer risk associated with body size is not clear. Hypotheses that link obesity to levels of estrogen, insulin, and insulin-like growth factor pathways have been proposed. However, an inflammation pathway may also be important, because adipose tissue is involved in production of cytokines, key elements in inflammation signaling (5,6).

Pro-inflammatory cytokines are secreted by adipose tissue, resulting in obesity being recognized as an “inflammatory state” (7) which, in turn, could influence cancer risk associated with obesity. Polymorphisms in the interleukin-6 (*IL6*) gene promoter have been reported to be related to the levels of circulating C-reactive protein (8), to be associated with different profiles of plasma IL-6 response to immunization (9), and to modify the association between high BMI and incident type 2 diabetes (10). Inflammation is accepted as a key component of the carcinogenic process (11). When a tumor cell loses its ability to control growth, a microenvironment typical of cell injury is established that is mediated by cytokines, chemokines, and enzymes which facilitate inflammation and tumor progression (12). These processes are thought to be important for the development and progression of breast tumors (13). It is possible that genotype regulates genetic susceptibility and response to inflammation.

In this study, we evaluated how IL-6 polymorphisms influence the association of body size and breast cancer risk among women living in the Southwestern United States. We have shown previously that allele frequencies differ among several IL-6 single nucleotide polymorphisms between Hispanic/AI and NHW women living in the Southwest and that IL-6 polymorphisms influence breast cancer risk (14). Also, we observed a 30–50% reduced risk of breast cancer among women with a C allele of the rs1800795 and the G allele of the rs1800797 IL-6 markers; associations were slightly stronger for Hispanic women than for NHW women. On the basis of our previous observations, we hypothesized that variation in IL-6 influences breast cancer risk associated with body size in NHW and Hispanic/AI women. We evaluated five *IL6* single nucleotide polymorphisms in the *IL6* gene in conjunction with BMI during the referent year and at age 15, weight gain, and waist-to-hip ratio (WHR) to test our hypothesis.

METHODS AND PROCEDURES

Study participants were women living in the Arizona counties of Cochise, Coconino, Maricopa, Pima, Pinal, Santa Cruz, or Yuma; or the states of Colorado, New Mexico, or Utah at the time of diagnosis with breast cancer or date of selection as a control; AI women living on reservations were not eligible. All Hispanic women diagnosed with histologically confirmed *in situ* and invasive breast cancer (International Classification of Diseases-Oncology sites C50.0–C50.6 and C50.8–C50.9) between October 1999 and May 2004 were selected for the study to examine risk factors adequately for breast cancer among Hispanic women given the fewer number of incident breast cancer cases among Hispanic women in

die Southwestern United States. A 5-year, age-matched sample of NHW female breast cancer cases were randomly selected at the following ratios to the distribution of Hispanic cases: 1:1 in Arizona and Colorado; 4:1 in Utah; and 1:1 for women >50 years in New Mexico. For women aged ≤50 years in New Mexico, all Hispanic and NHW cases were selected. Controls were matched to cases on 5-year-age category and ethnicity. Controls aged <65 years were randomly selected from a commercial mailing list (Arizona, Colorado) or driver's license lists (New Mexico, Utah). In all states, controls aged ≥65 years were randomly selected from Centers for Medicare & Medicaid Services lists. A detailed description of study methods and response rates has been published (4). Of cases identified, 873 Hispanic/AI and 1,683 NHW women participated (68% of women contacted). Of these cases, 798 Hispanic/AI and 1,527 NHW women were diagnosed with first primary breast cancer. Of controls identified, 935 Hispanic/AI and 1,671 NHW women participated (42% of participants contacted). Participation rates were discussed in greater detail previously (4).

The GUESS program (Generally Useful Ethnic Search System) in conjunction with data from the US Census was used to identify both cases and controls with Hispanic surnames (15). All women selected for the study were screened for eligibility before study enrollment. As a part of the screening, women were asked to self-identify their race and ethnicity. Women initially identified as being Hispanic by the GUESS program who were subsequently found not to be Hispanic or AI were ineligible for the study. All participants signed an informed written consent form before participation; the study was approved by the Institutional Review Board for Human Subjects at the University of Arizona, University of Colorado, University of New Mexico, and University of Utah.

Diet and lifestyle data, including a weight history, were collected by trained and certified interviewers using an interviewer-administered computerized questionnaire (4). Information on weight at ages 15,30, and 50, number of times participants gained and lost 10 or more pounds, and birth weight were obtained. Height, waist, and hip circumference measurements were taken at die time of interview. BMI was calculated using the formula of weight in kilograms/height in meters $(m)^2$. An extensive physical activity questionnaire was administered as described previously (16–18). Menopausal status was determined from the questionnaire where women were asked to look at a response card and select the category that "best describes your menstrual status on (referent date)." HRT use and parity were ascertained. The referent period was the year before diagnosis for cases or selection for controls. Respondents were asked to self-identify their ethnicity and race as apart of the study questionnaire. If a respondent described herself as belonging to more than one race or ethnic group, all were recorded.

Genotyping

A blood sample was collected and DNA extracted for 76.6% of participants in Arizona, 74.8% of participants in Colorado, 75% percent of participants in New Mexico, and 93.6% of participants in Utah. IL-6 marker genotypes were obtained for: 1,174 first-primary cases and 1,329 controls (NHW); 555 cases and 683 controls (Hispanics); 21 cases and 43 controls (AIs). All markers were genotyped using TaqMan-based assays and were chosen based on previous publication of functional importance and availability of assays. Formarkers rs1800795 and rs1800797, assays were performed according to Watanabe (19). For marker rs 1800795, primers IL6-174F 5′-TAGCCTCAATGACGACCTAAGCT-3′and IL6-174R 5′ GGGCTGATTGGAAACCTTATTAAG-3′and probes IL6-174G 5′-VIC-TGTCTTGC(G)ATGCTA-MGB-3′and IL6-174C 5′-6FAM-TGTCTTGC(C)ATGCTA-MGB-3′ were used. For marker rs1800797, primers IL6-596F 5′-GCCTTGAAGTAACTGCACGAAATT-3′ and IL6-596R 5′-TGTTCTGGCTCTCCCTGTGA-3′and probes IL6-596G 5′-VIC-CCTGGCCA(C)CCTCA-MGB-3′ and IL6-596A 5′-6FAM-CTGGCCA(T)CCTCA-MGB-3′ were used. For markers

rs2069849, rs2069832, and rs1800796, complete assays were purchased from Applied Biosystems (Foster City, CA).

In brief, each 5 μl polymerase chain reaction contained 20 ng genomic DNA, 900nmol/l of each primer, 125 nmol/l of each TaqMan probe, and 2.5 μl TaqMan Universal PCR Master Mix (contains AmpErase UNG and AmpliTaq Gold enzymes, deoxyribonucleotide triphosphates, and reaction buffer). Polymerase chain reaction was carried out under the following conditions: 50 °C for 2 min to activate UNG, 95 °C for 10min, followed by 40 cycles of 92°C for 15 s, and 60 °C for 1 min using a 384-well dual block ABI 9700. Fluorescence endpoint of tile TaqMan reaction was measured using a 7900HT sequence detection instrument. Control samples representing all three possible genotypes were included at four positions in every 384-well tray. In addition, internal replicates representing >1% of the sample set were blinded and included; concordance was 100%. The call rate was 99.6% for rs1800795, 99.7% for rs1800796, 99.2% for rs1800797, and 99.3% for rs1800796.

Statistical methods

The SAS version 9.1 (Cary, NC, 2002) statistical package was used to conduct the analyses. Subjects who reported Hispanic ethnicity, exclusively or in combination with any other racial or ethnic group, were included as Hispanic. As the number of participants reporting only AI ancestry was small and the fact that they often reported Hispanic and AI ethnicity, AI women were combined with women who self-identified as being Hispanic for race/ethnicity-stratified analyses. Previous assessment of genetic admixture in this population lends support to this categorization (20).

Both genotypes and haplotypes were evaluated for five *IL6* markers. We used genotype data from control subjects, considering NHW and Hispanic/AI women separately, to estimate population haplotype frequencies and to infer chromosomal phase of linked loci in study subjects. We employed the expectation–maximization algorithm (21,22), implemented in SAS/Genetics software (Cary, NC, 2002), to develop maximum likelihood estimates of population haplotype frequencies. The algorithm converges on haplotype frequencies that have the highest probability of generating the observed genotypes. Fifteen *IL6* haplotypes with an estimated population frequency of >0.0001 in NHW subjects were possible, based on the five polymorphisms considered. Haplotype dose variables were estimated in each subject to assign the probability of carrying particular pairs of *IL6* haplotypes, based on observed individual genotypes and predicted population haplotype frequencies (23). In homozygotes and women heterozygous for one marker, haplotype dose assignment was unambiguous; either 0 (haplotype was not possible based on the subjects genotypes), 1 (heterozygosity), or 2 copies (homozygosity for a particular haplotype). When assignment was ambiguous (individuals heterozygous for >1 polymorphism), haplotype dose variables (non-integer, range between 0 and 2 copies) were based on the probability of each haplotype given an individuals observed genotypes and estimated population frequencies. For each subject, the dose summed across IL-6 haplotypes equals two. These probabilities can be used in regression models to evaluate disease association (24).

We evaluated the combined associations of genetic polymorphisms with body size variables using analysis of covariance tests; P values of ≤0.05 were considered significant, as study hypothesis and design focused a priori on menopausal and ethnicity stratification. We evaluated the joint effect of genotypes and haplotypes and BMI (kg/m^2) during the referent year, BMI at age 15, weight gain from age 15 to the referent year, and WHR. As risk estimates were similar for heterozygous and homozygous genotypes for the minor allele, those groups were combined and compared with homozygous wildtype for dominant inheritance models. Multivariable logistic regression models were used to estimate odds

ratios (ORs) adjusting for age, center, parity, long-term physical activity, and percent of AI ancestry based on genetic admixture (20); BMI was adjusted in models assessing the association between WHR and breast cancer risk. ORs with 95% confidence intervals (CIs) that did not include 1 were considered significant. Genetic admixture was determined by analyzing 15 markers selected to distinguish between AI and European ancestry and the program STRUCTURE which was used to estimate percent of AI ancestry based on these genetic markers. These methods have been described in detail (20). The proportion of admixture, as determined by affiliation to either NHW or Hispanic population, was entered into logistic models to adjust more fully for AI ancestry among Hispanic participants. Haplotype dose variables for the four most common haplotypes, with a combined population frequency >97%, were included as continuous variables in logistic regression models to estimate ORs for the association between the haplotypes and the breast cancer, adjusting for covariates (25).

Data were analyzed according to self-reported race/ethnicity, i.e., NHW or Hispanic/AI, and menopausal status. Among postmenopausal women, we evaluated differences in association between those who were recently exposed to hormones, either by becoming postmenopausal within 2 years of the referent year or by receiving HRT, and those who were not. To model the interaction of exposure and haplotype, ORs were calculated for each category of exposure and number of copies of a particular haplotype (0, 1, or 2) with the lowest category of exposure and 0 copies of the haplotype as the reference group (25). Effect modification between genotypes (assuming a dominant model) or haplotype dose and exposure category variables was determined by evaluating the improvement in model fit (difference in −2 log likelihood values) of a model including a multiplicative interaction term compared to a restricted model with no interaction term; *P* values of ≤0.05 were considered significant.

RESULTS

Hispanic/AI women were slightly younger than NHW (Table 1). The majority of women were postmenopausal. Approximately, 71% of NHW and 64% of Hispanic/AI postmenopausal women had recent hormone exposure either through recent menopause or HRT use before the referent year.

Table 2 shows the minor allele frequency of each of the *IL6* markers for NHW and Hispanic/AI controls. Three of the *IL6* markers (rs 1800797 and rs 1800795 in the 5′ promoter region, and intronic single nucleotide polymorphism rs2069832) are in high pairwise Lewontin's D′ (Lewontin's D′ > |0.98|, $r^2 > 0.90$). Two haplotypes accounted for an estimated 90% of alleles in NHW and three haplotypes accounted for an estimated 90% of alleles in Hispanic/AI women. For NHW, mean level of BMI decreased across minor allele genotypes for *IL6* rs1800797, rs1800795, and rs2069832, although the trend did not reach statistical significance (*P* values 0.06 and 0.07). Among Hispanic/AI women, mean level of BMI was not associated with any of the *IL6* markers examined. Evaluation of mean levels of BMI for the four most common haplotypes (shown as *IL6* alleles, in order: rs1800797, rs1800796, rs1800795, rs2069832, and rs2069849) indicated more copies of the GGCAC haplotype, i.e., minor alleles for rs1800797, rs1800795, and rs2069832 were associated with lower mean BMIs; this was significant only among NHW. Mean WHR was associated with only the rs1800796 marker, and haplotype ACGGC that included the variant rs1800796 C allele, in NHW women (*P* trend 0.02 and 0.03, respectively). Mean levels of WHR among Hispanic/AI women did not vary with *IL6* genotype.

Joint associations of *IL6* genotypes and body size on breast cancer risk are shown in Tables 3 and 4. Associations were similar for BMI during the referent year, BMI at age 15, and weight gain; therefore, data are presented only for BMI during the referent year (Table 3)

and WHR (Table 4). As results were similar to the three markers in high Lewontin's D′, data are presented for one of these markers, rsl800795 (−174 G>C), in addition to rs1800796 (−572 G>C, also known as −634 C>G). There were no significant interactions between rs1800795 or the rs1800796 marker and BMI in either NHW or Hispanic/AI women; there also were no significant interactions between BMI and IL-6 haplotypes.

WHR interacted with the rs1800795 *IL6* marker among NHW postmenopausal women (Table 4). Among NHW women, having a large WHR, increased breast cancer risk in the presence of the rs1800795 GG genotype, while having a C allele suggested a reduced risk of breast cancer. Associations of the *IL6* rs1800796 marker and WHR in breast cancer risk among postmenopausal women recently exposed to hormones differed by ethnicity. Among NHW women, having a C allele was associated with a reduced risk of breast cancer among women with the largest WHR (OR 0.24 95% CI 0.05–1.16), while among Hispanic/AI women having a C allele was associated with an increased risk of breast cancer among women with the largest WHR (OR 2.05 95% CI 0.84,5.02).

Further assessment of *IL6* haplotypes was consistent with genotype results (Table 5). Homozygosity for the most common haplotype (AGGGC), containing the rs1800795 G allele, was associated with increased risk of breast cancer in NHW postmenopausal women with WHR >0.9. Likewise, homozygosity for the haplotype containing the variant rs1800795 C allele was protective in NHW women with the largest WHR (*P* interaction 0.01).

DISCUSSION

The association between body size and breast cancer is complex given the inverse association between obesity and breast cancer risk among premenopausal women and a direct association between obesity and breast cancer risk among post-menopausal women, particularly those who are not exposed to postmenopausal hormones (4). We have shown previously that among Hispanic/AI women, obesity is associated with reduced breast cancer risk for both pre- and post-menopausal women (4). The reasons for these associations are not clear, but most likely involve a combination of factors that include hormonal and possibly an inflammation-related pathway. It has been estimated that about one-third of circulating levels of IL-6 in healthy individuals is derived from adipose tissue (26). From previous analyses, we know that there are different allele frequencies between NHW and Hispanic women for common polymorphisms of the *IL6* gene (14). Although we hypothesized that genetic variation in the *IL6* gene may account for differences in risk associated with BMI between Hispanic and NHW women, our data provide little support for this hypothesis. Although some variation in breast cancer risk was observed by *IL6* genotype and haplotype in conjunction with WHR, this association was generally observed only for NHW women.

The *IL6* polymorphisms examined in the study have been shown to be associated with indicators of inflammation, obesity, and diabetes (27), suggesting that they may be functional, although findings are not universal (28). The C allele of the −572G>C (rs1800796) polymorphism and G allele of the −174G>C (rs1800795) polymorphism in the *IL6* gene promoter have been related to higher levels of circulating C-reactive protein and serum IL-6 (8,9,29). Others have shown that the CC genotype of the −174G>C (rs1800795) polymorphism was associated with increased obesity (30,31). In an examination of functional effects of polymorphisms (including −572G>C and −174G>C) and haplotypes in the *IL6* promoter area of the gene, Terry *et al.* reported haplotypes showed functional differences that suggest the combination of base changes at multiple sites influences function (32). We observed a non-significant linear trend toward lower levels of obesity in

conjunction with the minor C allele of the −174G>C variant (rs1800795), and the two markers in linkage disequilibrium with this marker, −596A>G (rs 1800797) and IVS2G>A (rs2069832) *(P* linear trend of 0.07, 0.06, and 0.07, respectively). However, an evaluation of haplotypes showed that NHW women who carry 1 or 2 copies of the haplotype with minor alleles for rs1800797, rs1800795, and rs2069832, i.e., GGCAC, had significantly lower BMI levels *(P* linear trend 0.02). We did not observe any significant associations for the Hispanic/AI women in our study. This may reflect limited power among Hispanic/AI women as the estimated frequency of this haplotype is considerably less than what we observed among NHW women.

Although we observed trends in association between level of BMI and *IL6* GGCAC haplotype, we generally did not observe difference in risk of breast cancer associated with IL-6 genotype and haplotype among obese women. As serum levels of IL-6 are influenced by adipose tissue, variation in amount of inflammatory cytokines produced as a consequence of genotype would alter the inflammatory state and could subsequently alter breast cancer risk. Our data suggest that these associations may be restricted to central adiposity given our association with WHR. IL-6 is known to increase the expression of aromatase in breast cancer cells, thereby enhancing the conversion of androgens to estrogens (33). Variation in the *IL6* gene may regulate this conversion. Central adiposity has been associated with metabolic syndrome and insulin resistance (34). Epidemiological studies show strong associations between systemic markers of inflammation such as IL-6, and a heightened risk for obesity-related insulin resistance (35–38). Our data suggest that women at higher risk for metabolic syndrome given their large WHR are also at greater risk of breast cancer dependent on their *IL6* genotype, possibly because of greater risk for insulin resistance. However, for the most part, these associations are limited to NHW women.

This study has limitations. Although our sample of Hispanic cases is large, it is still limited in size to examine genetic factors in conjunction with lifestyle factors for pre- and post-menopausal women. It is unknown whether the differences in association between Hispanic/AI women and NHW women are the result of limited power, differential recall of key risk factors, or differences in metabolic factors between the two ethnic groups, Although our matching ratios of Hispanic and NHW differed by center, we do not believe that this would influence results because all adjustment variables were collected in the same manner and sampling was independent of genotype. Although we know that Hispanic/AI women were more likely to report obesity at an early age (4), the long-term consequences of early adiposity are not well understood. We also recognize that the few associations and interactions we observed in our investigation of specific study hypotheses may reflect chance, because a number of comparisons were made; thus replication in other populations is important to confirm or disprove our results.

In summary, our data suggest that *IL6* polymorphisms influence level of BMI and appear to modulate breast cancer risk associated with WHR among NHW women. These findings need replication, particularly in Hispanic/AI women, to obtain a better understanding of breast cancer risk factors in that population.

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Table 1

Description of study population

	Non-hispanic white				Hispanic/AI			
	Cases		Controls		Cases		Controls	
	N	%	*N*	%	*N*	%	*N*	%
Total	1,176	46.9	1,330	53.1	576	44.2	727	55.8
Center								
Arizona	165	14.0	263	19.8	116	20.1	164	22.6
Colorado	237	20.2	218	16.4	112	19.4	132	18.2
New Mexico	464	39.5	496	37.3	252	43.8	250	34.4
Utah	310	26.4	353	26.5	96	16.7	181	24.9
Age								
25–39	74	6.3	101	7.6	58	10.1	82	11.3
40–49	348	29.6	347	26.1	199	34.5	204	28.1
50–59	334	28.4	352	26.5	165	28.6	194	26.7
60–69	283	24.1	300	22.6	108	18.8	167	23.0
70–79	137	11.6	230	17.3	46	8.0	80	11.0
Menopause status								
Pre/peri	415	35.3	415	31.2	238	41.3	266	36.6
Post	761	64.7	915	68.8	338	58.7	461	63.4
Recent hormone exposure, postmenopausal women								
Yes	539	70.8	601	65.7	215	63.6	275	59.7
No	222	29.2	314	34.3	123	36.4	186	40.3

AI, American Indian.

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Table 2

Association between mean BMI (kg/m^2) and WHR levels and *IL6* genotypes and haplotypes in control subjects

			NHW mean BMI[a]				Hispanic/AI mean BMI[a]			
			Minor allele genotype				Minor allele genotype			
	NHW MAF	Hisp./AI MAF	0 Alleles	1 Allele	2 Alleles	Trend *P* value	0 Alleles	1 Allele	2 Alleles	Trend *P* value
IL-6 genotype										
rs1800797–596A>G	43.2	19.3	28.5	28.5	27.4	0.06	30.3	30.2	28.8	0.45
rs1800796–572G>C	5.5	25.6	28.2	29.1	28.5	0.14	29.9	30.8	29.1	0.64
rs1800795–174G>C	44.4	20.2	28.4	28.6	27.4	0.07	30.3	30.1	28.7	0.34
rs2069832 IVS2G>A	44.4	20.5	28.4	28.5	27.4	0.07	30.3	30.1	29.2	0.37
rs2069849 exon 5 C>T	2.3	6.6	28.2	28.7	26.5	0.63	30.3	29.8	37.8	0.91
IL-6 haplotype[b]	Freq.[b]	Freq.[b]	0 Copies	1 Copy	2 Copies		0 Copies	1 Copy	2 Copies	
AGGGC	47.7	47.5	27.8	28.5	28.2	0.34	30.1	30.2	30.4	0.75
GG**CA**C	42.7	19.1	28.7	28.3	27.4	**0.02**	30.3	30.2	28.8	0.45
A**C**GGC	5.3	25.4	28.2	29.1	28.4	0.14	30.0	30.9	28.9	0.68
AGGG**T**	2.1	6.6	28.3	28.0	–	0.75	30.3	29.8	37.8	0.91

			NHW mean WHR[a]				Hispanic/AI mean WHR[a]			
			Minor allele genotype			Trend *P* value	Minor allele genotype			Trend *P* value
			0 Alleles	1 Allele	2 Alleles		0 Alleles	1 Allele	2 Alleles	
IL-6 genotype										
rs1800797–596 A>G			0.80	0.81	0.79	0.88	0.84	0.83	0.86	0.36
rs1800796–572 G>C			0.80	0.81	0.81	0.03	0.84	0.84	0.85	0.68
rs1800795–174 G>C			0.80	0.81	0.79	0.71	0.84	0.83	0.86	0.52
rs2069832 IVS2 G>A			0.80	0.81	0.79	0.66	0.84	0.83	0.86	0.48
rs2069849 exon 5 C>T			0.80	0.81	0.80	0.42	0.84	0.83	0.86	0.25
IL-6 haplotype[b]			0 Copies	1 Copy	2 Copies		0 Copies	1 Copy	2 Copies	
AGGGC			0.80	0.81	0.79	0.41	0.84	0.84	0.84	0.51
GGC**A**C			0.80	0.81	0.79	0.68	0.84	0.83	0.86	0.50
A**C**GGC			0.80	0.81	0.81	**0.03**	0.84	0.84	0.85	0.62

			NHW mean BMI[a]				Hispanic/AI mean BMI[a]			
			Minor allele genotype				Minor allele genotype			
	NHW MAF	Hisp./AI MAF	0 Alleles	1 Allele	2 Alleles	Trend *P* value	0 Alleles	1 Allele	2 Alleles	Trend *P* value
AGGG**T**			0.80	0.81	–	0.43	0.84	0.83	0.86	0.25

AI, American Indian; MAF, minor allele frequency (%); NHW, non-hispanic white; WHR, waist-to-hip ratio.

[a]Adjusted for age at selection (continuous), age of menarche (<12, 12. 13, 14+), and parity (0, 1–2, 3–4, 5+).

[b]Order of interleukin-6 (IL-6) markers in haplotypes are: rs1800797, rs1800796, rs1800795, rs2069832, and rs2069849; minor allele shown in bold font.

[c]Estimated haplotype frequency (%).

Table 3

Interaction between *IL6* (rs1800795 and rs1800796) and referent year BMI (kg/m^2) and risk of breast cancer[a]

		Non-Hispanic White						Hispanic/American Indian					
		GG			GC/CC			GG			GC/CC		
		Cases	Controls	95% CI	Cases	Controls	95% CI	Cases	Controls	95% CI	Cases	Controls	95% CI
Marker	**BMI**	***N***	***N***	**OR (lower, upper)**	***N***	***N***	**OR (lower, upper)**	***N***	***N***	**OR (lower, upper)**	***N***	***N***	**OR (upper, lower)**
IL-6rs1800795													
Postmenopausal women, no recent hormone exposure													
	<25	28	29	1.00	37	84	0.43 (0.22,0.83)	20	21	1.00	7	13	0.53 (0.16,1.79)
	25–<30	32	41	0.75 (0.37, 1.54)	47	63	0.72 (0.37, 1.40)	36	37	1.17 (0.52, 2.63)	8	28	0.27 (0.09, 0.77)
	≥30	29	33	0.90 (0.43, 1.88)	49	61	0.74 (0.38, 1.44)	36	53	0.86 (0.39, 1.91)	16	33	0.54 (0.22, 1.33)
	P interaction						0.19						0.25
Postmenopausal women, recent hormone exposure													
	<25	87	84	1.00	155	180	0.84 (0.58, 1.22)	46	47		26	27	0.97 (0,49, 1.94)
	25–<30	62	46	1.32 (0.81, 2.15)	106	120	0.88 (0.59, 1.31)	53	63	0.88 (0.50, 1.53)	29	39	0.75 (0.40, 1.42)
	≥30	43	51	0.82 (0.49, 1.38)	84	119	0.69 (0.46, 1.05)	39	65	0.64 (0.36, 1.13)	21	33	0.66 (0.33, 1.32)
	P interaction						0.71						0.91
Premenopausal women													
	<25	82	61	1.00	157	163	0.76 (0.50,1.14)	52	64		37	31	1.56 (0.84, 2.91)
	25–<30	42	34	0.99 (0.56, 1.76)	59	75	0.62 (0.38, 1.00)	63	63	1.23 (0.73, 2.09)	16	28	0.70 (0.34, 1.46)
	≥30	25	28	0.71 (0.37, 1.35)	47	52	0.67 (0.39, 1.14)	44	46	1.32 (0.74, 2.35)	26	33	0.96 (0.50, 1.85)
	P interaction						0.65						0.09
IL-6rs1800796													
Postmenopausal women, no recent hormone exposure													
	<25	56	104	1.00	9	9	2.32 (0.85, 6.36)	23	23	1.00	4	11	0.25 (0.06, 1.03)
	25–<30	67	89	1.38 (0.87, 2.21)	12	15	1.56 (0.67, 3.63)	22	35	0.60 (0.26, 1.39)	22	30	0.73 (0.31,1.70)
	≥30	68	80	1.55 (0.96, 2.50)	10	14	1.41 (0.57, 3.45)	31	48	0.70 (0.32, 1.53)	21	38	0.56 (0.24, 1.31)
	P interaction						0.37						0.14
Postmenopausal women, recent hormone exposure													
	<25	218	238	1.00	25	26	0,99 (0.55, 1.79)	47	38	1.00	25	37	0,49 (0.25, 0.98)
	25–<30	148	152	1.07 (0.80, 1.44)	20	14	1.63 (0.80, 3.34)	45	57	0.61 (0.34, 1.10)	37	45	0.65 (0.35, 1.21)

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		Non-Hispanic White						Hispanic/American Indian					
		GG			GC/CC			GG			GC/CC		
		Cases	Controls	95% CI	Cases	Controls	95% CI	Cases	Controls	95% CI	Cases	Controls	95% CI
Marker	**BMI**	***N***	***N***	**OR (lower, upper)**	***N***	***N***	**OR (lower, upper)**	***N***	***N***	**OR (lower, upper)**	***N***	***N***	**OR (upper, lower)**
	≥30	109	148	0.81 (0.59, 1.11)	18	22	0.88 (0.46, 1.70)	30	50	0.48 (0.26, 0.92)	30	48	0.49 (0.25, 0.93)
	P interaction						0.65						0.19
Premenopausal women													
	<25	210	206	1.00	31	18	1.64 (0.88, 3.06)	55	61	1.00	34	34	1.11 (0.60, 2.07)
	25–<30	82	95	0.87 (0.61, 1.25)	19	14	1.32 (0.63, 2.74)	42	49	0.96 (0.54, 1.71)	37	42	0.93 (0.51, 1.70)
	≥30	64	71	0.86 (0.57, 1.28)	9	9	1.05 (0.40, 2.76)	38	44	0.99 (0.55, 1.78)	32	34	1.10 (0.58, 2.09)
	P interaction						0.89						0.93

CI, confidence interval; IL-6, irtterteukin-6; OR, odds ratio.

[a]Adjusted for age, center, parity, long-term physical activity, and percent American Indian ancestry (AI).

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Table 4

Interaction between IL-6 (rs1800795 and rs1800796) and waist-to-hip ratio (WHR) and risk of breast cancer[a]

		Non-hispanic white						Hispanic/AI					
		GG			GC/CC			GG			GC/CC		
		Cases	Controls	95% CI	Cases	Controls	95% CI	Cases	Controls	95% CI	Cases	Controls	95% CI
Marker	**Exposure**	***N***	***N***	**OR (lower, upper)**	***N***	***N***	**OR (lower, upper)**	***N***	***N***	**OR (lower, upper)**	***N***	***N***	**OR (lower upper)**
IL-6 rs1800795													
Postmenopausal women, no recent hormone exposure													
	<0.8	27	38	1.00	43	88	0.68 (0.36, 1.28)	17	17	1.00	9	17	0.30 (0.10, 0.96)
	0.8–0.9	42	55	1.15 (0.59, 2.24)	73	89	1.27 (0.68, 2.35)	56	69	0.73 (0.32, 1.67)	15	41	0.35 (0.14, 0.93)
	>0.9	20	11	3.22 (1.27, 8.17)	17	33	0.65 (0.29, 1.46)	19	25	0.81 (0.30, 2.17)	7	17	0.38 (0.11, 1.27)
	P interaction						0.01						0.78
Postmenopausal women, recent hormone exposure													
	<0.8	92	97	1.00	188	211	0.95 (0.67,1.34)	32	47	1.00	23	32	1.01 (0.49, 2.06)
	0.8–0.9	76	72	1.12 (0.72,1.75)	134	167	0.85 (0.58, 1.25)	82	100	1.33 (0.76, 2.33)	43	55	1.29 (0.69, 2.42)
	>0.9	24	13	2.01 (0,95, 4.27)	23	41	0.59 (0.32, 1,09)	24	28	1.59 (0.76, 3.36)	10	12	1.46 (0.54, 3.96)
	P interaction						0.04						0.99
Premenopausal women													
	<0.8	92	82	1,00	173	190	0.85 (0.59,1.23)	46	51	1.00	28	34	0.98 (0.50,1.89)
	0.8–0.9	49	38	1.45 (0.83, 2.53)	79	90	0.86 (0.55,1.36)	94	101	1.16 (0.69, 1.96)	40	46	1.06 (0.58, 1.96)
	>0.9	8	3	2.66 (0.66, 10.78)	11	11	0.99 (0.38, 2.56)	19	22	1.25 (0.56, 2.79)	11	12	1.22 (0.46, 3.25)
	P interaction						0.39						0.99
IL-6 rs1800796													
Postmenopausal women, no recent hormone exposure													
	<0.8	64	117	1.00	6	9	1.46 (0.48, 4.49)	15	19	1.00	11	15	0.80 (0.26, 2.44)
	0.8–0.9	99	122	1.59 (1.02,2.48)	16	22	1.64 (0.77, 3.46)	43	65	0.89 (0.38, 2,09)	28	45	0,88 (0.34, 2.24)
	>0.9	28	37	1.40 (0.75, 2.63)	9	7	2.60 (0.89, 7.57)	18	23	1.25 (0.44, 3.54)	8	19	0.59 (0.19, 1.87)
	P interaction						0.66						0.54
Postmenopausal women, no recent hormone exposure													
	<0.8	255	282	1.00	26	26	1.07 (0.60, 1.90)	30	39	1.00	25	40	0.78 (0.39, 1.59)
	0.8–0.9	175	212	0.91 (0.69, 1.20)	35	27	1.47 (0.85, 2.54)	76	80	1.37 (0.75, 2.48)	49	76	0.92 (0.49,1.73)

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		Non-hispanic white						Hispanic/AI					
		GG			GC/CC			GG			GC/CC		
		Cases	Controls	95% CI	Cases	Controls	95% CI	Cases	Controls	95% CI	Cases	Controls	95% CI
Marker	**Exposure**	***N***	***N***	**OR (lower, upper)**	***N***	***N***	**OR (lower, upper)**	***N***	***N***	**OR (lower, upper)**	***N***	***N***	**OR (lower upper)**
	>0.9	45	45	1.11 (0.69,1.78)	2	9	0.24 (0.05,1.16)	16	26	0.98 (0.43, 2.24)	18	14	2.05 (0.84,5.02)
	P interaction						0.03						0.11
Premenopausal women													
	<0.8	226	246	1.00	40	26	1.56 (0.91,2.66)	41	55	1.00	33	30	1.34 (0.69, 2.61)
	0.8–0.9	113	115	1.15 (0.81,1.63)	17	13	1.87 (0.85, 4.10)	75	81	1.28 (0.74, 2.20)	59	65	1.32 (0.73, 2.37)
	>0.9	17	12	1.61 (0.70, 3.68)	2	2	1.39 (0.19, 10.25)	19	18	1.70 (0.73, 3.93)	11	16	1.09 (0.42, 2.79)
	P interaction						0.86						0.49

CI, confidence interval; IL-6, interleukin-6; OR, odds ratio.

[a]Adjusted for age, center, partiy, long-term physical activity, BMI, and American Indian ancestry (AI).

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Table 5

Association between IL-6 hapiotypes and waist-to-hip ratio (WHR) and risk of breast cancer among postmenopausal women[a]

		No recent hormone exposure			Recent hormone exposure		
		0 Copies	1 Copy	2 Copies	0 Copies	1 Copy	2 Copies
Haplotype[b]	WHR	95%CI OR (lower, upper)	95%CI OR (lower, upper)	95%CI OR (lower, upper)	95%CI OR (lower, upper)	95%CI OR (lower, upper)	95%CI OR (lower, upper)
AGGGC							
NHW							
	<0.8	1.00	1.27 (0.84, 1.92)	1.62 (0.71, 3.71)	1.00	1.09 0.87, 1.37)	1.18 (0.75, 1.87)
	0.8–0.9	2.12 (1.04, 4.28)	1.99 (1.09, 3.65)	1.87 (0.92, 3.81)	1.04 (0.68, 1.61)	1.05 (0.74, 1.49)	1.06 (0.68, 1.66)
	>0.9	0.92 (0.31, 2.73)	1.94 (0.93, 4.03)	4.08 (1.50, 11.10)	0.37 (0.16, 0.86)	1.00 (0.60, 1.69)	2,74 (1.25, 6.00)
	P interaction			0.14			0.01
Hispanic/AI							
	<0.8	1.00	1.26 (0.60, 2.67)	1.60 (0.36, 7.11)	1.00	1,12 0.66, 1.93)	1.26 (0.43, 3.71)
	0.8–0.9	0.68 (0.22, 2.07)	1.09 (0.42, 2.84)	1.75 (0.62, 4.93)	1.10 (0.53, 2.25)	1.49 (0.79, 2.82)	2.02 (0.97, 4.24)
	>0.9	0.64 (0.17, 2.39)	1.21 (0.41, 3.52)	2.27 (0.63, 8.22)	2.64 (0.92, 7.56)	1.79 (0.83, 3.89)	1.22 (0.45, 3.33)
	P interaction			0.76			0.20
GG**CA**C							
NHW							
	<0.8	1.00	0.73 (0.48, 1.11)	0.53 (0.23, 1.23)	1.00	0.95 0.76, 1.20)	0.90 (0.57, 1.44)
	0.8–0.9	1.22 (0.66, 2.22)	1.20 (0.69, 2.07)	1.18 (0.58, 2.39)	1.02 (0.68, 1.51)	0.91 (0.65, 1.27)	0.82 (0.51, 1.30)
	>0.9	2.35 (1.02, 5.43)	0.87 (0.42, 1.82)	0.32 (0.09, 1.14)	1.79 (0.90, 3.56)	0.73 (0.43, 1.25)	0.30 (0.11, 0.80)
	P interaction			0.06			0.05
Hispanic/AI							
	<0.8	1.00	0.58 (0.21, 1.61)	0.34 (0.04, 2.58)	1.00	1.15 0.64, 2.07)	1.33 (0.41, 4.29)
	0.8–0.9	0.92 (0.42, 1.99)	0.52 (0.21, 1.26)	0.29(0.07, 1.16)	1.32 (0.77, 2.28)	1.54 (0.85, 2.77)	1.79 (0.74, 4.33)
	>0.9	0.92 (0.36, 2.33)	0.72 (0.26, 2.02)	0.56 (0.10, 3.07)	1.75 (0.84, 3.64)	1.56 (0.64, 3.79)	1.39 (0.29, 6.76)
	P interaction			0.84			0.86
A**C**GGC							
NHW							
	<0.8	1.00	1.54 (0.49, 4.85)	2.37 (0.24, 23.51)	1.00	1.11 0.65, 1.92)	1.24 (0.42, 3.68)

		No recent hormone exposure			Recent hormone exposure		
		0 Copies	1 Copy	2 Copies	0 Copies	1 Copy	2 Copies
Haplotype[b]	WHR	95%CI OR (lower, upper)	95%CI OR (lower, upper)	95%CI OR (lower, upper)	95%CI OR (lower, upper)	95%CI OR (lower, upper)	95%CI OR (lower, upper)
	0.8–0.9	1.61 (1.03, 2.50)	1.53 (0.74, 3.17)	1,45 (0.37, 5.66)	0.91 (0.69, 1.20)	1.62 (0.93, 2.81)	2.88 (0.99, 8.41)
	>0.9	1.52 (0.81, 2.85)	2.18 (0.81, 5.91)	3.13(0.46, 21.50)	1.12 (0.70, 1.80)	0.24 (0.05, 1.18)	0.05 (0.00, 1.24)
	P interaction			0.70			0.04
Hispanic/AI							
	<0.8	1.00	1.11 (0.42, 2.95)	1.22 (0.17, 8.68)	1.00	0.95 0.55, 1.63)	0.89 (0.30, 2.66)
	0.8–0.9	0.97 (0.42, 2.24)	1.03 (0.43, 2.51)	1.10 (0.32, 3.74)	1.62 (0.90, 2.91)	1.03 (0.57, 1.84)	0.65 (0,29, 1.46)
	>0.9	1.24(0.45, 3.44)	0.92 (0.33, 2.53)	0.68(0.15, 3.11)	1.20 (0.54, 2.67)	1.95 (0.88, 4.30)	3.15 (0.85, 11.69)
	P interaction			0.73			0.07

CI, confidence interval; OR, odds ratio.

[a] Adjusted for age, center, parity, long-term physical activity, BMI, and American Indian (AI) ancestry.

[b] Order of lnterleukin-6 (IL-6) markers in haplotypes are: rs1800787, rs1800796, rs1800795, rs2069832, and rs2069849; minor allele shown in bold font.

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