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Genetic Variation in the JAK/STAT/SOCS signaling pathway influences breast cancer-specific mortality through interaction with cigarette smoking and use of aspirin/NSAIDs: The Breast Cancer Health Disparities Study

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Abstract

Purpose—The Janus kinase (JAK)/signal transducer and activator of transcription (STAT)-signaling pathway is involved in immune function and cell growth; genetic variation in this pathway could influence breast cancer risk.

Methods—We examined 12 genes in the JAK/STAT/SOCS-signaling pathway with breast cancer risk and mortality in an admixed population of Hispanic (2111 cases, 2597 controls) and non-Hispanic white (1481 cases, 1585 controls) women. Associations were assessed by Indigenous American (IA) ancestry.

Results—After adjustment for multiple comparisons, *JAK1* (3 of 10 SNPs) and *JAK2* (4 of 11 SNPs) interacted with body mass index (BMI) among pre-menopausal women, while *STAT3* (4 of 5 SNPs) interacted significantly with BMI among post-menopausal women to alter breast cancer risk. *STAT6* rs3024979 and *TYK2* rs280519 altered breast cancer-specific mortality among all women. Associations with breast cancer-specific mortality differed by IA ancestry; *SOCS1*

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rs193779, *STAT3* rs1026916, and *STAT4* rs11685878 associations were limited to women with low IA ancestry and associations with *JAK1* rs2780890, rs2254002, and rs310245 and *STAT1* rs11887698 were observed among women with high IA ancestry. *JAK2* (5 of 11 SNPs), *SOCS2* (1of 3 SNPs), and *STAT4* (2 of 20 SNPs) interacted with cigarette smoking status to alter breast-cancer specific mortality. *SOCS2* (1 of 3 SNPs) and all *STAT3*, *STAT5A*, and *STAT5B* SNPs significantly interacted with use of aspirin/NSAIDs to alter breast cancer-specific mortality.

Conclusions—Genetic variation in the JAK/STAT/SOCS pathway was associated with breast cancer-specific mortality. The proportion of SNPs within a gene that significantly interacted with lifestyle factors lends support for the observed associations.

Keywords

Breast Cancer; Breast cancer-specific mortality; JAK/STAT/SOCS; polymorphisms; BMI; cigarette smoking; aspirin/NSAIDs

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The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway is involved in immune function and cell growth and differentiation[1, 2]. The JAK family consists of four non-receptor protein tyrosine kinases, JAK1, JAK2, JAK3, and TYK2. Of these, JAK1, JAK2, and TYK2 are expressed ubiquitously in mammals [3]. Once activated by cytokines, JAKs serve as docking sites for signaling molecules such as STATs. Activated STATs translocate from the cytoplasm to the nucleus where they increase the transcription rate of several genes. STAT1 and STAT2 were first identified as contributing to activation of genes involved in immune response [4]. STAT5 was first described in the mammary gland and has considerable specificity for mammary gland development [5]. Altogether, seven STATS have been identified in mammalian cells, STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6 [6]. STAT signaling has been shown to be important for mammary cell survival and tumorigenesis [6]. It has also been suggested that expression of STATs are associated with unique breast cancer subtypes defined by estrogen receptor (ER) and progesterone receptor (PR) status [7].

Cytokines up-regulate suppressors of cytokine signaling (SOCS) that inhibit the activity of JAKs and STATs [8]. Thus, research targeting an understanding of the JAK/STAT/SOCS signaling pathway often has involved the interaction between JAK/STAT/SOCS with cytokines. STAT1 and STAT2 were first identified from work involving downstream events of receptor binding of interferon γ (IFNγ) on transcriptional activation of genes involved in immune response[4]. Pro-inflammatory cytokines, such as IL-6 have been shown to up-regulate STAT proteins [4, 9, 10]. Both JAK1 and JAK2 are important for cytokines through use of the shared receptor subunits; IL-6 is an important pro-inflammatory cytokine that uses these receptors since they are essential for cytokine signaling [11]. JAK2 is essential for hormone-like cytokine signaling, including prolactin signaling [11].

This study builds on our previous work that has evaluated breast cancer associations with genetic variants in cytokines among women with diverse genetic ancestry. We have shown that breast cancer risk and mortality as well as risk associated with *IL6* and other cytokine SNPs differ by Indigenous American (IA) ancestry [12, 13]. Thus, it is reasonable to hypothesize that breast cancer associations with genetic variation in JAK/STAT/SOCS

genes may also vary by IA ancestry. Given previous work that suggest these genes may have unique ER/PR associations, we evaluated associations by ER/PR tumor subtype. Additionally, we evaluated the association of these genes with survival since one of their functions is to promote cell differentiation and metastases [14]. Since diet and lifestyle factors that are associated with inflammation may modify associations with these genes, we evaluate interaction of these genes with a dietary oxidative balance score, body mass index (BMI), cigarette smoking status, and use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs).

Methods

The Breast Cancer Health Disparities Study includes participants from three population-based case-control studies [15], the 4-Corners Breast Cancer Study (4-CBCS) [16], the Mexico Breast Cancer Study (MBCS)[17], and the San Francisco Bay Area Breast Cancer Study (SFBCS) [18, 19], who completed an in-person interview and who had a blood or mouthwash sample available for DNA extraction. Information on exposures was collected up to the referent year, defined as the calendar year before diagnosis for cases or before selection into the study for controls. 4-CBCS participants were between 25 and 79 years; MBCS participants were between 28 and 74 years; and SFBCS participants were between 35 to 79 years. All participants signed informed written consent prior to participation; the Institutional Review Board for Human Subjects at each institution approved the study.

Data Harmonization

Data were harmonized across all study centers and questionnaires as previously described [15]. Women were classified as either pre-menopausal or post-menopausal based on responses to questions on menstrual history. Pre-menopausal women were those who reported still having periods during the referent year. Post-menopausal women were those who reported either a natural menopause or if they reported taking hormone therapy (HT) and were still having periods or were at or above the 95th percentile of age for those who reported having a natural menopause (i.e., ≥ 12 months since their last period). Women in 4-CBCS and SFBCS were asked to self-identify their race/ethnicity and were classified as non-Hispanic white (NHW), Hispanic, Native American (NA) or a combination of these groups. Women in MBCS were not asked their race or ethnicity and were combined with U.S. Hispanics/NAs in the analyses.

Lifestyle variables included BMI calculated as self-reported weight (kg) during the referent year divided by measured height squared (m^2) and categorized as normal (<25 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥30 kg/m^2). Regular cigarette smoking was evaluated as current, former, or never, where regular was defined as having smoked one or more cigarettes for six months or longer in 4-CBCS and SFBCS (data available for a subset of subjects only) or having smoked 100 or more cigarettes in MCBCS. A dietary oxidative balance score (DOBS) that included nutrients with anti- or pro-oxidative properties was used [20]. Dietary information was collected via a computerized validated diet history questionnaire in 4-CBCS [12, 21], a 104-item semi-quantitative Food Frequency Questionnaire (FFQ) in MBCS [22], and a modified version of the Block Food Frequency

Questionnaire in SFBCS [23]. Alcohol consumption was based on long-term use; consumption during the referent year was used for a subset of SFBCS women without information on long-term use. Regular use of aspirin or NSAIDS defined as three or more times a week for at least one month was available for the 4-CBCS only. A history of diabetes was defined as ever being told by a health care provider that you had diabetes or high blood sugar (not available for all SFBCS participants).

Genetic Data

DNA was extracted from either whole blood (n=7287) or mouthwash (n=634) samples. Whole genome amplification (WGA) was applied to the mouthwash-derived DNA samples prior to genotyping. TagSNPs were selected to characterize the genetic variation using the following parameters: linkage disequilibrium (LD) blocks were defined using a Caucasian LD map and an r^2=0.8; minor allele frequency (MAF) >0.1; range= −1500 bps from the initiation codon to +1500 bps from the termination codon; and 1 SNP/LD bin. Additionally, 104 Ancestry Informative Markers (AIMs) were used to distinguish European and Indigenous American (IA) ancestry [15]. All markers were genotyped using a multiplexed bead array assay format based on GoldenGate chemistry (Illumina, San Diego, California. In the current analysis we evaluated tagSNPs for *JAK1* (10 SNPs), *JAK2* (11 SNPs), *SOCS1* (2 SNPs), *SOCS2* (3 SNPs), *STAT1* (15 SNPs), *STAT2* (2 SNPs), *STAT3* (5 SNPs), *STAT4* (20 SNPs), *STAT5A* (2 SNPs), *STAT5B* (3 SNPs), *STAT6* (6 SNPs), *TYK2* (4 SNPs). Online Supplement 1 provides a description of these genes and SNPs; online supplement 2 describes LD structure of these genes.

Tumor Characteristics and Survival

Data on estrogen receptor (ER) and progesterone receptor (PR) tumor status and survival were available for cases from 4-CBCS and SFBCS only. Cancer registries in Utah, Colorado, Arizona, New Mexico, and California provided information on stage at diagnosis, months of survival after diagnosis, cause of death, and ER and PR status. Surveillance Epidemiology and End Results (SEER) disease stage was categorized as local, regional, or distant.

Statistical Methods

Genetic ancestry estimation—The program STRUCTURE was used to estimate individual ancestry for each study participant assuming two founding populations [24, 25]. A three-founding population model was assessed but did not fit the population structure. Participants were classified by level of percent IA ancestry (≤28%, >28–70%, and >70%), based on the distribution of genetic ancestry in the control population [15].

SNP Associations—Genes and SNPs were assessed for their association with breast cancer risk overall, by strata of IA ancestry, and by menopausal status in the whole population and by ER/PR status for the 4-CBCS and SFBCS. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for breast cancer risk associated with SNPs, adjusting for study, BMI in the referent year, and parity as categorical variables and age (five-year categories) and genetic ancestry as continuous

variables. Associations with SNPs were assessed assuming a co-dominant model. Based on the initial assessment, SNPs that appeared to have a dominant or recessive mode of inheritance were evaluated with those inheritance models in subsequent analyses. For stratified analyses, the p value was based on the Wald chi-square test comparing the homozygote rare to the homozygote common when presenting the co-dominant model. The multinomial p value reported for ER/PR status using the glogit link in the logistic procedure compares unique associations by tumor phenotype. Adjustments for multiple comparisons within the gene used the step-down Bonferroni correction, taking into account the degree of correlation of the SNPs within genes using the SNP spectral decomposition method proposed by Nyholt [26] and modified by Li and Ji [27]. An unadjusted p value of <0.05 was considered statistically significant; results are presented for those where the multiple comparison adjusted p value was <0.15 and are noted as being marginally associated.

Interactions—We assessed gene by environment interactions for lifestyle factors that could influence candidate genes given their potential involvement in inflammation, including BMI (separately for pre- and post-menopausal women given differences in risk associated with BMI by menopausal status), smoking (current, former, or never smokers), dietary oxidative balance score (DOBS), and regular use of aspirin/NSAID (for 4-CBCS participants only). DOBS was based on each individual's intake of anti-oxidants (vitamin C, vitamin E, beta carotene (data for beta carotene were not available for MBCS), folic acid, and dietary fiber) and pro-oxidants (alcohol). Nutrients were evaluated per 1000 calories and the DOBS was based on study-specific distributions given the different dietary questionnaires used. Alcohol consumption was classified into three levels: the top 25^{th} percentile of consumption, all other drinkers, and non-drinkers. The DOBS ranges from low levels (first quartile) of exposure to anti-oxidants or high exposure to pro-oxidants (fourth quartile) to high levels of anti-oxidants (fourth quartile) and low exposure to pro-oxidants (non-drinkers). Tests for interactions were evaluated using Wald one degree of freedom (1-df) chi-square tests.

Survival Analysis—Survival months were calculated based on month and year of diagnosis and month and year of death or last contact. Survival updates were received in the winter of 2013 that included complete survival surveillance through December of 2012. Associations between SNPs and breast cancer-specific mortality among cases with a first primary invasive breast cancer were evaluated using Cox proportional hazards models to obtain multivariate hazard ratios (HR) and 95% confidence CI. Individuals were censored when they died of causes other than breast cancer or were lost to follow-up. We present Wald p values for all women and by ancestry strata based on the comparison between the homozygote rare and common genotype when presenting the co-dominant inheritance model using models adjusted for age, study center, genetic ancestry, and SEER stage. Since survival data were not available for MBCS, the upper two ancestry strata were combined to evaluate survival by genetic ancestry. Interactions between genetic variants and genetic ancestry, BMI, cigarette smoking, DOBS, and aspirin/NSAID use with survival were assessed using p values from 1-df Wald chi-square tests.

Results

The majority of women were U.S. Hispanic or Mexican and were slightly younger than U.S. NHW women (Table 1). U.S. Hispanic women were more likely to have ER−/PR− tumors than NHW women. Approximately 20% of women had died, with 47.6% of deaths being from breast cancer among NHW and 55.9% of deaths among U.S. Hispanic women.

Few associations were observed between SNPs in our candidate genes and breast cancer risk (Table 2). *STAT5B* rs6503691 and *TYK2* rs280519 were associated with reduced risk among women with high IA ancestry ($OR_{CT/TT}$ = 0.63 95% CI 0.41, 0.97, P_{het}=0.39 and $OR_{AG/GG}$ = 0.75 95% CI = 0.58, 0.96, P_{het}=0.46) and *STAT6* rs3024974 ($OR_{CT/TT}$ = 1.15 95 %CI 1.02, 1.29, P_{het}=0.71) was associated with increased breast cancer risk overall. More associations were observed for specific tumor phenotype, with *JAK2* rs1536800 being associated with ER−/PR− tumors and *STAT3* (4 SNPs) and *STAT5A* (2 SNPs) and *STAT5B* (1 SNP) associated with ER−/PR+ tumors. These differences were statistically significant for *JAK2* rs1536800 (P_{het}=0.03), *STAT3* rs8069645 (P_{het}=0.03), *STAT5A* 7217728 (P_{het}=0.04), and *STAT5B* rs7218653 (P_{het}=0.02). No significant differences in association were detected by menopausal status (data not shown).

BMI was the main lifestyle factor that interacted with these genes to alter risk of breast cancer (Table 3). *JAK1* (3 SNPs) and *JAK2* (4 SNPs) interacted with BMI among pre-menopausal women, with the majority of the differences observed among those who were obese. Among post-menopausal women, *STAT3* (4 SNPs) interacted with BMI to alter breast cancer risk, with the majority of the differences observed among those with normal BMI. Additionally, interactions were seen between *STAT1* (2 SNPs) and *STAT4* (1 SNP) and DOBS. We also assessed interaction between *IL6* and its receptor and JAK/STAT/SOC pathway genes and observed several significant interactions although after adjustment for multiple comparisons none of the associations were statistically significant (data not shown).

STAT6 rs3024979 and *TYK2* rs280519 were associated with breast cancer-specific mortality overall (Table 4). However, most associations were restricted to either low or high IA ancestry group. Among women with low IA ancestry, *SOCS1* rs193779, *STAT3* rs1026916, and *STAT4* rs11685878 were associated with breast cancer-specific mortality. Among women with high IA ancestry (*JAK1* rs2780890, rs2254002, and rs310245) and *STAT1* rs11887698 were associated with breast cancer-specific mortality. Additionally, *JAK2* (5 SNPs), *SOCS2* (1 SNP), and *STAT4* (2 SNPs) interacted with cigarette smoking status to alter breast cancer-specific mortality (Table 5), with associations predominantly observed among current smokers. *STAT1* rs2030171 and *STAT5B* rs9900213 interacted with DOBS to alter breast cancer-specific mortality (Table 5). Interactions also were seen between *SOCS2* (1 SNP), *STAT3* (5 SNPs), *STAT5A* (2 SNPs), and *STAT5B* (3 SNPs) and regular use of aspirin/NSAIDs. No significant interactions with BMI were observed after adjustment for multiple comparisons.

Discussion

Among genes within the JAK/STAT/SOC-signaling pathway, we observed several associations between SNPs and breast cancer mortality, and a few significant associations with risk of breast cancer, irrespective of genetic ancestry or ER/PR tumor subtypes. However, lifestyle factors that influence inflammation interacted with these genes to alter breast cancer risk and mortality. Specifically, BMI and DOBS interacted with these genes to alter breast cancer risk, while cigarette smoking and aspirin/NSAID use interacted with them to influence breast cancer-specific mortality. The proportion of SNPs within a gene that significantly interacted with DOBS and lifestyle factors was considerably greater than by chance, lending support for the observed associations.

Although it is reasonable to genes could help explain differences in breast cancer incidence rates when comparing populations with high vs. low IA ancestry, our results provide little support for that hypothesis. Others have suggested that this pathway has unique associations with tumor phenotype and estrogen [7, 28–30], but we found minimal support for differences in associations by ER/PR subtype. The majority of associations were with ER −/PR+ tumors, and although statistically significant after adjustment for multiple comparisons, there were few individuals with that phenotype and therefore estimates of association were imprecise even though they were statistically significant.

Of interest are the consistent associations observed for the interaction of BMI with *JAK1* (3 out of 10 SNPs) and *JAK2* (4 out of 11 SNPs) for pre-menopausal breast cancer risk and with *STAT3* (4 of 5 SNPs) for post-menopausal breast cancer risk. The number of SNPs within genes that were associated with breast cancer risk was greater than one would expect by chance. One explanation for the interactions between BMI and *JAK1*, *JAK2*, and *STAT3* could be the strong correlation between leptin and BMI. Although leptin is mainly produced by white adipocytes, it is also produced by mammary epithelium. The leptin receptor is a class I cytokine receptor that acts through JAK and STATs and the JAK/STAT pathway is one of the main signaling cascades activated by leptin [31]. Additionally, STAT3 specifically has been shown to influence energy homeostasis [32, 33]. Activation of the JAK/STAT pathway also can promote tumor growth and induce inflammation as well as regulate other genes that control cell proliferation, differentiation, tumor development, and cell survival.

The JAK/STAT pathway is critical for cell development, cell survival, cell proliferation, and apoptosis; our results suggest genetic variation in these genes is important for breast cancer-specific mortality. We observed stronger estimates of association and more consistent associations across genes, and SNPs within those genes, with breast cancer-specific mortality than with breast cancer risk. Thus, it is possible that these genes function as tumor promoters, as has been suggested [6, 34]. The strongest and most consistent associations were observed for the interaction between cigarette smoking and aspirin/NSAID use with *JAK2*, *STAT3*, *STAT5a*, and *STAT5b* and to a lesser extent with *SOSC2* (rs3816997 which interacted with both cigarette smoking and aspirin/NSAIDs use) to influence breast cancer-specific mortality. The JAK/STAT signaling pathway is activated when cytokines are bound to their receptors while SOCs suppresses the signaling. Nicotine has been shown to activate

the JAK2/STAT3 pathway [35], which in this case appears to promote tumor progression depending on *JAK2/STAT3* genotype.

Regular use of aspirin/NSAIDs interacted with all SNPs evaluated for *STAT3* (5), *STAT5A* (2), and *STAT5B* (3) to alter breast cancer-specific mortality. STAT3 has been shown to be a promoter of tumor invasiveness and angiogenesis [6]. Activation of STAT5, which was first recognized as mammary gland factor, results in regulation of several genes involved in cell apoptosis, survival, and proliferation [14]. It has been shown that aspirin regulates apoptosis by down-regulating the IL6-STAT3 pathway [36] and that the epidermal growth factor induces COX2 through STAT5 signaling [37] thus providing biological support for our observations.

We believe that these findings are unique and have found no reference to the importance of these genes in the literature or in GWAS studies of breast cancer. Our candidate pathway approach has enabled us to identified important genes based on their biological function. Furthermore our ability to evaluate interaction with diet and lifestyle factors has enhanced our understanding of these genes and how they influence breast cancer risk and mortality.

This study has both strengths and limitations. The population represents a large genetically diverse population that includes extensive data on diet and lifestyle factors along with genetic data, ER/PR status, and vital status. However, ER/PR status and vital status were available only for the U.S. based studies. We used a tag-SNP approach to characterize genetic variation in these genes, although other SNPs could be important that were not analyzed. We adjusted for multiple comparisons within our candidate genes, although we cannot exclude the possibility of chance observations. However, the number of SNPs within genes for which we observed associations further indicates that these observations may be more than chance findings. Nevertheless, we encourage others to replicate our findings, especially those that pertain to survival, given their implication for treatment modalities as has been suggested [38].

In conclusion, our findings suggest that genetic variation in the JAK/STAT/SOCS signaling pathway is important for breast cancer-specific mortality. Of note is the consistent and stronger interaction observed between *JAK2*, *SOCS2*, *STAT3* and *STAT5* and cigarette smoking and use of aspirin/NSAIDs to modify breast cancer-specific mortality. Additionally *JAK1, JAK2, and STAT3* interacted with BMI to modify risk of developing breast cancer. Given the potential importance of these findings on modalities such as aspirin/NSAIDS to improve survival on a subset of women, replication of these findings in other populations is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Description of study population by self-reported race/ethnicity

	U.S. non-Hispanic White				U. S. Hispanic/Native American or Mexican			
	Controls		Cases		Controls		Cases	
	N	%	N	%	N	%	N	%
Total	1585	37.9	1481	41.2	2597	62.1	2111	58.8
Study Site								
4-CBCS	1321	83.3	1227	82.8	723	27.8	597	28.3
MBCS	0	0	0	0	994	38.3	816	38.7
SFBCS	264	16.7	254	17.2	880	33.9	698	33.1
Age (years)								
<40	116	7.3	89	6	311	12	200	9.5
40–49	408	25.7	409	27.6	831	32	713	33.8
50–59	409	25.8	413	27.9	756	29.1	617	29.2
60–69	349	22	361	24.4	526	20.3	430	20.4
>70	303	19.1	209	14.1	173	6.7	151	7.2
Mean	56.6		56		52.3		52.7	
Menopausal Status								
Pre-menopausal	494	31.5	489	33.5	1027	40.7	836	40.9
Post-menopausal	1075	68.5	970	66.5	1499	59.3	1210	59.1
Estimated Percent Indigenous American Ancestry								
0–28	1577	99.5	1472	99.4	278	10.7	275	13
29–70	7	0.4	7	0.5	1686	64.9	1393	66
71–100	1	0.1	2	0.1	633	24.4	443	21
ER/PR Status[2]								
ER+/PR+	NA[1]		695	68.2	NA[1]		605	61.9
ER+/PR−	NA[1]		121	11.9	NA[1]		115	11.8
ER−/PR+	NA[1]		15	1.5	NA[1]		28	2.9
ER−/PR−	NA[1]		188	18.4	NA[1]		229	23.4
SEER Summary Stage[2,3]								

	U.S. non-Hispanic White				U. S. Hispanic/Native American or Mexican			
	Controls		Cases		Controls		Cases	
	N	%	N	%	N	%	N	%
Local	NA[1]		830	70.9	NA[1]		650	59.6
Regional	NA[1]		325	27.8	NA[1]		432	39.6
Distant	NA[1]		15	1.3	NA[1]		9	0.8
Vital Status[2,3]								
Deceased	NA[1]		254	21.4	NA[1]		229	19.8
Alive	NA[1]		935	78.6	NA[1]		929	80.2
Cause of Death[2,3]								
Breast Cancer	NA[1]		121	47.6	NA[1]		128	55.9
Other	NA[1]		133	52.4	NA[1]		101	44.1
Smoking Status[4]								
Never	794	60.3	688	56.1	1616	72.1	1298	70.1
Former	360	27.3	386	31.5	347	15.5	322	17.4
Current	163	12.4	152	12.4	278	12.4	231	12.5
BMI (kg/m^2)								
<25	699	44.4	678	45.9	453	17.6	492	23.5
25–29.9	465	29.5	433	29.3	951	36.9	768	36.7
>30	412	26.1	367	24.8	1172	45.5	832	39.8
NSAID use[5]								
No	708	53.7	670	54.7	446	61.7	395	66.2
Yes	610	46.3	554	45.3	277	38.3	202	33.8
Dietary Oxidative Balance Score[6][mean (SD)]								
4-CBCS	6.3 (2.7)		6.3 (2.6)		6.7 (2.5)		6.5 (2.6)	
MCBCS	NA[1]		NA[1]		5.9 (2.0)		5.7 (2.0)	
SFBCS	5.6 (2.6)		5.7 (2.6)		6.9 (2.5)		6.1 (2.5)	

[1] Data not applicable (NA)

[2] Data unavailable from Mexico Breast Cancer Study (MBCS)

[3]Includes first primary invasive breast cancer cases from the 4-Corners Breast Cancer Study (4-CBCS) and San Francisco Bay Area Breast Cancer Study (SFBCS)

[4]Data unavailable from women using questionnaire's one and two from SFBCS

[5]Data only available for the 4-CBCS

[6]Dietary Oxidative Balance Score (DOBS) includes alcohol (pro-oxidant), vitamin C, vitamin E, beta carotene (data not available for MCBCS), folic acid, and dietary fiber (anti-oxidants).

Table 2

Associations between JAK/STAT genes and risk of breast cancer by genetic ancestry and Estrogen and Progesterone Receptor Tumor Phenotype.

	Overall			≤28% IA Ancestry			>28–70% IA Ancestry			>70% IA Ancestry		
	Controls	**Cases**	**OR[2] (95% CI)**	**Controls**	**Cases**	**OR (95% CI)**	**Controls**	**Cases**	**OR (95% CI)**	**Controls**	**Cases**	**OR (95% CI)**
STAT5B (rs6503691)												
CC	3378	2897	1.00	1473	1383	1.00	1350	1115	1.00	555	399	1.00
CT/TT	779	672	0.98 (0.87, 1.10)	374	359	1.01 (0.86, 1.19)	331	275	1.01 (0.84, 1.21)	74	38	0.63 (0.41, 0.97)
P-value (raw; adjusted)			0.713, 1.000			0.906, 0.906			0.938, 1.000			0.035, 0.069
STAT6 (rs3024974)												
CC	3435	2868	1.00	1507	1394	1.00	1384	1097	1.00	544	377	1.00
CT/TT	720	698	1.15 (1.02, 1.29)	340	346	1.10 (0.93, 1.30)	295	292	1.25 (1.04, 1.50)	85	60	1.01 (0.70, 1.46)
P-value (raw; adjusted)			0.018, 0.072			0.268, 1.000			0.017, 0.068			0.953, 1.000
TYK2 (rs280519)												
AA	1499	1265	1.00	476	439	1.00	681	562	1.00	342	264	1.00
AG/GG	2651	2289	0.96 (0.87, 1.06)	1371	1295	1.03 (0.89, 1.20)	995	821	0.98 (0.84, 1.13)	285	173	0.75 (0.58, 0.96)
P-value (raw; adjusted)			0.416, 1.000			0.704, 1.000			0.766, 1.000			0.025, 0.093
	ER+/PR+			ER+/PR−			ER−/PR+			ER−/PR−		
JAK2 (rs1536800)												
CC	1798	764	1.00	122		1.00	26		1.00	263		1.00
CT/TT	1374	533	0.92 (0.81, 1.05)	113		1.22 (0.93, 1.59)	17		0.85 (0.46, 1.57)	152		0.75 (0.61, 0.93)
P-value (raw; adjusted)			0.225, 1.000			0.150, 0.899			0.595, 1.000			0.009, 0.053
STAT3 (rs8069645)[1]												
AA	1872	756	1.00	133		1.00	18		1.00	253		1.00
AG	1119	468	1.00 (0.87, 1.15)	94		1.16 (0.88, 1.53)	19		1.91 (0.99, 3.68)	144		0.96 (0.77, 1.20)
GG	181	74	0.94 (0.70, 1.25)	8		0.58 (0.28, 1.21)	6		3.79 (1.46, 9.84)	18		0.74 (0.44, 1.22)
P-value (raw; adjusted)			0.785, 0.959			0.831, 1.000			0.004, 0.010			0.324, 0.882
STAT3 (rs6503695)												
TT	1662	672	1.00	117		1.00	17		1.00	222		1.00
TC	1256	519	0.98 (0.85, 1.12)	106		1.17 (0.88, 1.55)	19		1.63 (0.83, 3.19)	164		0.99 (0.79, 1.23)

	Overall			≤28% IA Ancestry			>28–70% IA Ancestry			>70% IA Ancestry		
	Controls	**Cases**	**OR[2] (95% CI)**	**Controls**	**Cases**	**OR (95% CI)**	**Controls**	**Cases**	**OR (95% CI)**	**Controls**	**Cases**	**OR (95% CI)**
CC	255	106	0.93 (0.73, 1.19)	12		0.62 (0.33, 1.14)	7		3.10 (1.23, 7.81)	28		0.83 (0.54, 1.26)
P-value (raw; adjusted)			0.564, 0.959			0.687, 1.000			0.016, 0.029			0.507, 0.882
STAT3 (rs12949918)												
TT	1428	578	1.00	109		1.00	13		1.00	197		1.00
TC	1371	573	0.98 (0.85, 1.13)	97		0.90 (0.67, 1.21)	23		2.07 (1.03, 4.19)	171		0.92 (0.73, 1.15)
CC	372	147	0.88 (0.71, 1.10)	29		0.95 (0.61, 1.47)	7		2.47 (0.94, 6.47)	46		0.91 (0.64, 1.29)
P-value (raw; adjusted)			0.344, 0.959			0.631, 1.000			0.030, 0.030			0.454, 0.882
STAT3 (rs1026916)												
GG	1550	636	1.00	119		1.00	14		1.00	215		1.00
GA/AA	1622	662	0.96 (0.84, 1.09)	116		0.91 (0.69, 1.19)	29		2.13 (1.11, 4.09)	200		0.90 (0.73, 1.11)
P-value (raw; adjusted)			0.522, 0.959			0.488, 1.000			0.024, 0.029			0.317, 0.882
STAT5A (rs7217728)[1]												
TT	1836	740	1.00	130		1.00	16		1.00	247		1.00
TC/CC	1335	557	0.99 (0.87, 1.13)	105		1.09 (0.83, 1.43)	27		2.5 (1.32, 4.72)	168		0.94 (0.76, 1.17)
P-value (raw; adjusted)			0.920, 0.920			0.533, 0.835			0.005, 0.007			0.600, 0.600
STAT5A (rs12601982)												
AA	2364	945	1.00	174		1.00	26		1.00	320		1.00
AG/GG	806	353	1.06 (0.91, 1.22)	61		1.00 (0.74, 1.36)	17		2.03 (1.08, 3.80)	95		0.88 (0.69, 1.12)
P-value (raw; adjusted)			0.479, 0.750			0.980, 0.980			0.027, 0.027			0.294, 0.461
STAT5B (rs7218653)[1]												
AA	1849	745	1.00	132		1.00	15		1.00	237		1.00
AG/GG	1323	553	1.00 (0.87, 1.14)	103		1.07 (0.81, 1.40)	28		2.85 (1.49, 5.43)	178		1.07 (0.86, 1.32)
P-value (raw; adjusted)			0.946, 0.958			0.631, 0.631			0.002, 0.003			0.541, 0.541

[1] p values for difference by ER/PR group after adjustment for multiple comparisons were 0.07, 0.05, and 0.04 respectively

[2] Odds ratios (OR) and 95% confidence Intervals (CI) adjusted for age, study center, BMI during referent year, parity, and genetic ancestry. Risk estimates are shown in the table if one or more of the adjusted p values for multiple comparisons is <0.15.

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Table 3

Interaction between BMI, DOBS and JAK/STAT genes and risk of breast cancer

	Controls	Cases	OR[1] (95% CI)	Controls	Cases	OR (95% CI)	Controls	Cases	OR (95% CI)	
	Normal (< 25 kg/m^2)			Overweight (25 to <30 kg/m^2)			Obese (>= 30 kg/m^2)			Interaction P (raw; adjusted)
						Pre-menopausal				
JAK1 (rs4916005)										
TT	307	328	1.00	310	237	0.76 (0.60, 0.96)	277	241	0.89 (0.70, 1.13)	0.009, 0.054
TC	143	151	1.01 (0.76, 1.34)	180	147	0.86 (0.65, 1.14)	201	125	0.66 (0.49, 0.88)	
CC	17	33	1.98 (1.07, 3.67)	35	31	0.97 (0.57, 1.65)	46	25	0.60 (0.35, 1.01)	
JAK1 (rs310211)										
AA	188	212	1.00	165	115	0.66 (0.48, 0.90)	133	132	0.97 (0.70, 1.33)	0.009, 0.054
AG	205	207	0.93 (0.71, 1.23)	239	199	0.81 (0.61, 1.07)	247	187	0.76 (0.56, 1.01)	
GG	74	92	1.15 (0.79, 1.66)	121	99	0.85 (0.60, 1.21)	143	71	0.50 (0.35, 0.73)	
JAK1 (rs2256298)										
CC	225	247	1.00	202	143	0.69 (0.52, 0.92)	167	152	0.91 (0.68, 1.22)	0.027, 0.106
CT	187	197	1.02 (0.77, 1.34)	229	193	0.85 (0.65, 1.13)	241	179	0.77 (0.58, 1.02)	
TT	55	68	1.19 (0.79, 1.78)	94	79	0.91 (0.63, 1.33)	116	60	0.54 (0.37, 0.79)	
JAK2 (rs10974916)										
GG	228	245	1.00	260	196	0.76 (0.58, 0.99)	231	202	0.90 (0.68, 1.18)	0.018, 0.074
GA	201	216	1.01 (0.77, 1.32)	224	183	0.83 (0.63, 1.09)	233	159	0.71 (0.53, 0.94)	
AA	38	51	1.31 (0.82, 2.07)	41	36	0.90 (0.55, 1.48)	60	30	0.51 (0.32, 0.83)	
JAK2 (rs7043371)										
AA	120	148	1.00	127	106	0.74 (0.51, 1.05)	155	94	0.55 (0.39, 0.79)	0.024, 0.074
AT	241	248	0.86 (0.64, 1.16)	280	207	0.66 (0.48, 0.89)	261	192	0.66 (0.48, 0.91)	
TT	106	116	0.88 (0.61, 1.26)	118	102	0.76 (0.53, 1.10)	108	105	0.87 (0.60, 1.26)	
JAK2 (rs1536800)										
CC	264	283	1.00	295	227	0.77 (0.60, 0.99)	254	228	0.93 (0.72, 1.20)	0.001, 0.008
CT	184	191	0.98 (0.75, 1.28)	203	166	0.83 (0.63, 1.09)	226	143	0.64 (0.49, 0.85)	
TT	19	38	1.96 (1.10, 3.50)	26	21	0.85 (0.46, 1.56)	44	20	0.47 (0.27, 0.83)	
JAK2 (rs3780381)										

	Controls	Cases	OR[1] (95% CI)	Controls	Cases	OR (95% CI)	Controls	Cases	OR (95% CI)	
	Normal (< 25 kg/m^2)			Overweight (25 to <30 kg/m^2)			Obese (>= 30 kg/m^2)			Interaction P (raw; adjusted)
AA	228	256	1.00	274	199	0.70 (0.54, 0.90)	225	211	0.92 (0.70, 1.20)	0.009, 0.045
AC	205	206	0.90 (0.69, 1.17)	216	182	0.81 (0.62, 1.07)	241	150	0.61 (0.46, 0.81)	
CC	34	50	1.36 (0.85, 2.19)	34	34	0.98 (0.58, 1.64)	58	30	0.50 (0.31, 0.82)	
	Post-Menopause									
STAT3 (rs8069645)										
AA	376	383	1.00	545	468	0.91 (0.75, 1.10)	640	463	0.78 (0.64, 0.94)	0.025, 0.026
AG	256	218	0.82 (0.65, 1.04)	269	256	0.96 (0.76, 1.20)	340	275	0.85 (0.68, 1.06)	
GG	38	27	0.66 (0.40, 1.11)	48	36	0.74 (0.47, 1.16)	43	38	0.90 (0.57, 1.43)	
STAT3 (rs6503695)										
TT	320	329	1.00	502	430	0.90 (0.73, 1.10)	592	424	0.76 (0.62, 0.93)	0.012, 0.026
TC	291	257	0.83 (0.66, 1.05)	297	284	0.95 (0.75, 1.19)	371	297	0.82 (0.66, 1.02)	
CC	59	42	0.64 (0.41, 0.98)	64	46	0.67 (0.44, 1.01)	60	55	0.92 (0.62, 1.38)	
STAT3 (rs12949918)										
TT	271	288	1.00	435	372	0.86 (0.69, 1.07)	531	381	0.74 (0.59, 0.92)	0.009, 0.026
TC	308	277	0.81 (0.64, 1.02)	340	316	0.89 (0.71, 1.12)	398	321	0.79 (0.63, 0.99)	
CC	91	63	0.60 (0.42, 0.86)	88	72	0.72 (0.51, 1.03)	92	74	0.78 (0.55, 1.11)	
STAT3 (rs1026916)										
GG	317	337	1.00	461	390	0.85 (0.69, 1.05)	549	407	0.76 (0.62, 0.94)	0.047, 0.047
GA/AA	353	291	0.75 (0.60, 0.94)	402	370	0.89 (0.72, 1.10)	473	369	0.78 (0.63, 0.96)	
	DOBS Low			DOBS Intermediate			DOBS High			
STAT1 (rs1400657)										
AA	784	831	1.00	1781	1488	0.81 (0.72, 0.91)	784	587	0.72 (0.63, 0.84)	0.006, 0.065
AC/CC	182	150	0.76 (0.60, 0.97)	388	306	0.75 (0.63, 0.90)	154	145	0.90 (0.70, 1.15)	
STAT1 (rs3771300)										
CC	321	359	1.00	746	567	0.69 (0.57, 0.83)	344	240	0.64 (0.51, 0.80)	0.014, 0.126
CA	450	428	0.81 (0.66, 0.99)	1044	889	0.75 (0.63, 0.89)	438	349	0.69 (0.56, 0.85)	
AA	195	195	0.82 (0.63, 1.05)	378	337	0.76 (0.62, 0.94)	153	143	0.80 (0.61, 1.06)	
STAT4 (rs925847)										
CC	491	561	1.00	1204	922	0.69 (0.59, 0.80)	511	374	0.66 (0.55, 0.80)	0.003, 0.035

	Controls	Cases	OR[1] (95% CI)	Controls	Cases	OR (95% CI)	Controls	Cases	OR (95% CI)	
	Normal (< 25 kg/m^2)			Overweight (25 to <30 kg/m^2)			Obese (>= 30 kg/m^2)			Interaction P (raw; adjusted)
CT	390	357	0.80 (0.66, 0.97)	817	739	0.81 (0.69, 0.95)	353	301	0.75 (0.62, 0.92)	
TT	81	61	0.63 (0.44, 0.90)	143	131	0.81 (0.62, 1.05)	72	57	0.72 (0.50, 1.04)	

[1]Odds Ratios (OR) and 95% Confidence Intervals (CI) adjusted for age, study center, BMI during referent year (where appropriate), parity, and genetic ancestry. Risk estimates are shown in the table if the adjusted p value for multiple comparison is <0.15.

Table 4

Associations between breast cancer-specific mortality and JAK/STAT/SOC genes by genetic ancestry

	Overall		≤28% IA Ancestry		>28% IA Ancestry		
	Deaths/Person Years	**HR (95% CI)**	**Deaths/Person Years**	**HR (95% CI)**	**Deaths/Person Years**	**HR (95% CI)**	**Interaction P (raw; adjusted)**
JAK1 (rs2780890)							0.031, 0.123
AA/AG	182/17816	1.00	99/9601	1.00	83/8215	1.00	
GG	67/5942	1.19 (0.89, 1.59)	46/4600	0.96 (0.68, 1.36)	21/1342	1.84 (1.13, 3.00)	
P-value (raw; adjusted)		0.237, 0.950		0.823, 1.000		0.015, 0.058	
JAK1 (rs2254002)							0.019, 0.116
GG	91/7759	1.00	57/5631	1.00	34/2129	1.00	
GT/TT	158/15987	0.79 (0.61, 1.03)	88/8571	1.02 (0.73, 1.43)	70/7417	0.54 (0.36, 0.82)	
P-value (raw; adjusted)		0.088, 0.529		0.911, 1.000		0.004, 0.023	
JAK1 (rs310245)							0.024, 0.119
CC	90/7651	1.00	56/5499	1.00	34/2152	1.00	
CT/TT	159/16107	0.80 (0.61, 1.04)	89/8702	1.01 (0.72, 1.42)	70/7405	0.55 (0.36, 0.83)	
P-value (raw; adjusted)		0.090, 0.529		0.948, 1.000		0.005, 0.023	
SOCS1 (rs193779)							0.055, 0.104
GG	164/14841	1.00	93/8135	1.00	71/6706	1.00	
GA/AA	85/8876	0.87 (0.67, 1.14)	52/6040	0.70 (0.50, 0.99)	33/2836	1.19 (0.78, 1.81)	
P-value (raw; adjusted)		0.303, 0.570		0.045, 0.085		0.431, 0.431	
STAT1 (rs11887698)							0.025, 0.232
AA	139/12820	1.00	97/10015	1.00	42/2805	1.00	
AG	89/8187	0.91 (0.69, 1.22)	43/3677	1.17 (0.80, 1.70)	46/4509	0.65 (0.42, 0.99)	
GG	21/2741	0.62 (0.38, 1.03)	5/499	0.89 (0.36, 2.22)	16/2242	0.46 (0.25, 0.83)	
P-value (raw; adjusted)		0.063, 0.513		0.799, 0.799		0.010, 0.092	
STAT3 (rs1026916)							0.006, 0.018
GG	121/11584	1.00	51/6044	1.00	70/5540	1.00	
GA/AA	128/12174	1.04 (0.81, 1.34)	94/8157	1.44 (1.02, 2.03)	34/4017	0.67 (0.45, 1.02)	
P-value (raw; adjusted)		0.744, 1.000		0.039, 0.108		0.062, 0.157	
STAT4 (rs11685878)							0.011, 0.148
CC	104/8981	1.00	61/4679	1.00	43/4302	1.00	

	Overall		≤28% IA Ancestry		>28% IA Ancestry		
	Deaths/Person Years	**HR (95% CI)**	**Deaths/Person Years**	**HR (95% CI)**	**Deaths/Person Years**	**HR (95% CI)**	**Interaction P (raw; adjusted)**
CT	111/11114	0.88 (0.67, 1.16)	69/7167	0.76 (0.54, 1.07)	42/3947	1.08 (0.70, 1.65)	
TT	34/3651	0.86 (0.58, 1.27)	15/2343	0.55 (0.31, 0.97)	19/1308	1.49 (0.86, 2.58)	
P-value (raw; adjusted)		0.438, 1.000		0.039, 0.539		0.151, 1.000	
STAT6 (rs3024979)							0.531, 0.733
TT	195/19983	1.00	109/11477	1.00	86/8506	1.00	
TA/AA	53/3760	1.52 (1.12, 2.07)	35/2708	1.43 (0.97, 2.10)	18/1051	1.74 (1.04, 2.91)	
P-value (raw; adjusted)		0.008, 0.032		0.071, 0.167		0.033, 0.133	
TYK2 (rs280519)							0.866, 1.000
AA	93/7511	1.00	41/3505	1.00	52/4006	1.00	
AG	115/10927	0.97 (0.73, 1.28)	73/6753	0.99 (0.67, 1.46)	42/4174	0.91 (0.60, 1.38)	
GG	39/5187	0.67 (0.46, 0.98)	30/3863	0.69 (0.43, 1.11)	9/1324	0.57 (0.28, 1.17)	
P-value (raw; adjusted)		0.040, 0.147		0.130, 0.347		0.124, 0.455	

[1] Hazard Ratio (HR) and 95% Confidence Interval (CI) adjusted for age, study center, BMI during referent year, SEER summary stage, and genetic ancestry.

Risk estimates are shown in the table if one or more of the adjusted p values for multiple comparisons is <0.15.

Table 5

Interactions between cigarette smoking, DOBS, aspirin/NSAID and JAK/STAT/SOC genes and risk of breast cancer-specific mortality

	Deaths/Person Years	HR[1] (95% CI)	Deaths/Person Years	HR (95% CI)	Deaths/Person Years	HR (95% CI)	Interaction P (raw; adjusted)
	Never Smoker		Former Smoker		Current Smoker		
JAK2 (rs2274471)							0.008, 0.024
TT	73/6760	1.00	20/2545	0.73 (0.44, 1.20)	11/1074	0.99 (0.52, 1.87)	
TC/CC	37/4214	0.84 (0.56, 1.25)	14/2043	0.73 (0.41, 1.30)	24/1015	2.26 (1.41, 3.61)	
JAK2 (rs7043371)							0.024, 0.047
AA	21/3033	1.00	9/1192	0.96 (0.44, 2.10)	15/526	3.11 (1.59, 6.11)	
AT/TT	90/7935	1.57 (0.98, 2.54)	25/3396	1.14 (0.64, 2.05)	20/1563	2.05 (1.11, 3.79)	
JAK2 (rs10974947)							<.001, 0.003
GG	76/6702	1.00	17/2522	0.63 (0.37, 1.07)	11/1166	0.86 (0.45, 1.62)	
GA/AA	35/4275	0.75 (0.50, 1.13)	17/2065	0.78 (0.46, 1.34)	24/922	2.43 (1.52, 3.90)	
JAK2 (rs3780379)							0.002, 0.008
GG	83/7477	1.00	22/2910	0.73 (0.45, 1.17)	14/1333	0.99 (0.56, 1.75)	
GA/AA	28/3491	0.78 (0.51, 1.19)	12/1677	0.70 (0.38, 1.30)	21/756	2.65 (1.62, 4.32)	
JAK2 (rs10815160)							0.002, 0.008
TT	64/5649	1.00	18/2343	0.70 (0.41, 1.18)	8/1055	0.76 (0.36, 1.59)	
TG/GG	47/5328	0.78 (0.54, 1.14)	16/2244	0.67 (0.39, 1.17)	27/1034	2.16 (1.37, 3.42)	
SOCS2 (rs3816997)							0.028, 0.057
TT	73/7405	1.00	23/3073	0.80 (0.50, 1.28)	29/1335	2.27 (1.47, 3.50)	
TG/GG	38/3571	1.09 (0.73, 1.62)	11/1514	0.77 (0.41, 1.45)	6/754	0.83 (0.36, 1.91)	
STAT4 (rs4853546)							0.010, 0.137
GG	62/4918	1.00	13/1960	0.51 (0.28, 0.94)	12/962	1.06 (0.57, 1.98)	
GA/AA	49/6059	0.64 (0.44, 0.93)	21/2627	0.69 (0.42, 1.14)	23/1127	1.58 (0.97, 2.57)	
STAT4 (rs1031508)							0.010, 0.137
CC	67/5811	1.00	14/2500	0.46 (0.26, 0.82)	15/1157	1.20 (0.68, 2.10)	
CT/TT	44/5166	0.73 (0.50, 1.07)	20/2087	0.97 (0.58, 1.60)	20/932	1.78 (1.07, 2.96)	
	DOBS Low		DOBS Intermediate		DOBS High		
STAT1 (rs2030171)							0.008, 0.069

	Deaths/Person Years	HR[1] (95% CI)	Deaths/Person Years	HR (95% CI)	Deaths/Person Years	HR (95% CI)	Interaction P (raw; adjusted)
	Never Smoker		Former Smoker		Current Smoker		
GG	35/2447	1.00	48/3891	0.82 (0.53, 1.28)	12/1583	0.53 (0.27, 1.03)	
GA	31/2873	0.70 (0.43, 1.13)	62/5774	0.70 (0.46, 1.07)	16/2273	0.52 (0.28, 0.94)	
AA	8/1315	0.32 (0.15, 0.71)	25/2541	0.66 (0.39, 1.13)	11/948	0.87 (0.43, 1.75)	
STAT5B (rs9900213)							0.021, 0.041
GG	54/4998	1.00	100/8944	1.10 (0.79, 1.54)	35/3605	1.09 (0.71, 1.67)	
GT/TT	20/1680	1.32 (0.79, 2.23)	36/3299	1.14 (0.74, 1.74)	4/1206	0.34 (0.12, 0.93)	
	Non-Regular Aspirin/NSAID Users		Regular Aspirin/NSAID Users				
SOCS2 (rs3816997)							0.042, 0.083
TT	59/5410	1.00	40/3790	0.99 (0.66, 1.48)			
TG/GG	28/2283	1.16 (0.73, 1.83)	8/1619	0.46 (0.22, 0.96)			
STAT3 (rs1053005)							<.001, <.001
AA	66/5127	1.00	22/3604	0.45 (0.28, 0.74)			
AG/GG	21/2566	0.57 (0.35, 0.94)	26/1793	1.12 (0.71, 1.79)			
STAT3 (rs8069645)							0.014, 0.014
AA	53/4328	1.00	20/3009	0.51 (0.30, 0.86)			
AG/GG	34/3365	0.78 (0.50, 1.20)	28/2400	0.99 (0.62, 1.58)			
STAT3 (rs6503695)							0.006, 0.006
TT	50/3938	1.00	15/2471	0.44 (0.24, 0.79)			
TC/CC	37/3755	0.71 (0.46, 1.10)	33/2937	0.90 (0.57, 1.41)			
STAT3 (rs12949918)							0.003, 0.005
TT	44/3243	1.00	13/2202	0.40 (0.21, 0.75)			
TC	36/3653	0.75 (0.48, 1.17)	24/2397	0.78 (0.47, 1.30)			
CC	7/796	0.48 (0.21, 1.10)	11/810	0.99 (0.50, 1.95)			
STAT3 (rs1026916)							0.006, 0.006
GG	44/3549	1	14/2605	0.42 (0.23, 0.77)			
GA/AA	43/4144	0.84 (0.55, 1.29)	34/2803	1.04 (0.65, 1.65)			
STAT5A (rs7217728)							<.001, <.001
TT	66/4310	1.00	13/2709	0.28 (0.15, 0.52)			
TC/CC	21/3383	0.37 (0.22, 0.60)	35/2699	0.87 (0.57, 1.33)			

	Deaths/Person Years	HR[1] (95% CI)	Deaths/Person Years	HR (95% CI)	Deaths/Person Years	HR (95% CI)	Interaction P (raw; adjusted)
	Never Smoker		Former Smoker		Current Smoker		
STAT5A (rs12601982)							<.001, <.001
AA	70/5470	1.00	25/3805	0.49 (0.30, 0.77)			
AG/GG	17/2223	0.51 (0.30, 0.88)	23/1604	1.12 (0.69, 1.81)			
STAT5B (rs9900213)							0.050, 0.050
GG	70/5514	1.00	31/3886	0.64 (0.42, 0.98)			
GT/TT	17/2179	0.66 (0.39, 1.13)	17/1522	0.94 (0.55, 1.63)			
STAT5B (rs6503691)							0.002, 0.002
CC	78/5966	1.00	33/4215	0.59 (0.39, 0.89)			
CT/TT	9/1727	0.42 (0.21, 0.84)	15/1193	1.11 (0.64, 1.94)			
STAT5B (rs7218653)							<.001, <.001
AA	63/4307	1.00	13/2691	0.30 (0.16, 0.54)			
AG/GG	24/3386	0.43 (0.27, 0.70)	35/2718	0.90 (0.59, 1.37)			

[1]Hazard ratio (HR) and 95% confidence intervals (CI) adjusted for age, study center, BMI during referent year (where appropriate), genetic ancestry, and SEER stage.

Risk estimates are shown in the table if the adjusted p value for multiple comparison is <0.15.