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Diet and lifestyle factors interact with *MAPK* genes to influence survival: The Breast Cancer Health Disparities Study

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Abstract

Introduction—*MAPK* genes are activated by a variety of factors related to growth factors, hormones, and environmental stress.

Methods—We evaluated associations between 13 *MAPK* genes and survival among 1187 non-Hispanic white (NHW) and 1155 Hispanic/Native American women diagnosed with breast cancer. We assessed the influence of diet, lifestyle, and genetic ancestry on these associations. Percent Native American (NA) ancestry was determined from 104 Ancestry Informative Markers. Adaptive rank truncation product (ARTP) was used to determine gene and pathway significance.

Results—Associations were predominantly observed among women with lower NA ancestry. Specifically, the MAPK pathway was associated with all-cause mortality (P_{ARTP}=0.02), but not with breast cancer-specific mortality (P_{ARTP}=0.10). However, *MAP2K1* and *MAP3K9* were associated with both breast cancer-specific and all-cause mortality. *MAPK12* (P_{ARTP}=0.05) was only associated with breast cancer-specific mortality, and *MAP3K1* (P_{ARTP}=0.02) and *MAPK1* (P_{ARTP}=0.05) were only associated with all-cause mortality. Among women with higher NA ancestry, *MAP3K2* was significantly associated with all-cause mortality (P_{ARTP}=0.04). Several diet and lifestyle factors, including alcohol consumption, caloric intake, dietary folate, and

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Novelty: This study evaluates lifestyle and genetic factors that influence breast cancer survival. These factors are evaluated in a large genetically admixed population.

cigarette smoking, significantly modified the associations with *MAPK* genes and all-cause mortality.

Conclusions—Our study supports an association between *MAPK* genes and survival after diagnosis with breast cancer, especially among women with low NA ancestry. The interaction between genetic variation in the MAPK pathway with diet and lifestyle factors for all women supports the important role of these factors for breast cancer survivorship.

Keywords

Breast Cancer; Survival; MAPK; diet; alcohol; cigarette smoking

Introduction

Mitogen-activated protein kinases (MAPK) act as integration points for multiple biochemical signals and are involved in a variety of cellular processes, including cell proliferation, differentiation, transcription regulation and development [1]. Various environmental stimuli, cytokines, and hormones activate MAPK pathways. ERK1 and ERK2 are activated by stimuli such as growth factors and cytokines [1], while the JNK pathway is activated by radiation, environmental stresses, and growth factors. The JNK pathway has been shown to be involved in the development of obesity and type 2 diabetes [2, 3]. The *p38* MAPKs have been linked to autoimmunity in humans and are activated by chemical stresses, hormones, cytokines including IL-1 and TNF, and oxidative stress [1, 4].

Activation of MAPK in breast carcinoma has been shown to induce gene expression leading to increased proliferation, invasion and metastasis [5-7]. In this study, we examined the association between variants in *MAPK* genes and survival after diagnosis with breast cancer in non-Hispanic white (NHW) and U.S. Hispanic/Native American (NA) women, a genetically admixed population. Our analysis is motivated by the differences in breast cancer incidence and survival rates for these groups of women. Hispanic/NA women living in the Southwestern United States have lower incidence rates of breast cancer, although survival is slightly less. Given that *MAPK* genes are activated by a variety of factors related to growth factors, hormones, and environmental stress, we hypothesized that certain diet and lifestyle factors associated with activation of this signaling pathway would interact with genetic variation in *MAPK* genes to alter survival in women diagnosed with breast cancer. To our knowledge studies have not reported how MAPK genes relate to breast cancer survival and how diet and lifestyle factor influence those associations.

Methods

This analysis from the Breast Cancer Health Disparities Study includes participants with information on survival from two population-based case-control studies, the 4-Corners Breast Cancer Study (4-CBCS) and the San Francisco Bay Area Breast Cancer Study (SFBCS) [8]. In the 4-CBCS, participants were between 25 and 79 years of age, residents of Arizona, Colorado, New Mexico, or Utah with a histologically confirmed diagnosis of first primary invasive breast cancer (n=1391) between October 1999 and May 2004 [9]. The SFBCS included women aged 35 to 79 years from the San Francisco Bay Area diagnosed

with a first primary histologically confirmed invasive breast cancer (n= 946) between April 1997 and April 2002 [10, 11]. All participants signed informed written consent prior to participation; this study was approved by the Institutional Review Boards for Human Subjects at each participating institution.

Data Harmonization

Data were harmonized across study-specific questionnaires[8]. Women were considered post-menopausal if they 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); others were classified as pre-menopausal. Lifestyle variables included body mass index (BMI) calculated as self-reported weight (kg) during the referent year divided by measured height squared (m^2). Cigarette smoking was classified as ever versus never having smoked cigarettes on a regular basis (> than 100 cigarettes). Having a history of diabetes included those told by a doctor that they had diabetes or high blood sugar; in the SFBCS not all women were asked questions regarding diabetes and are excluded from that portion of the analysis. Dietary information was collected via a computerized validated diet history questionnaire for the 4-CBCS[12, 13] or a modified version of the Block Food Frequency Questionnaire for the SFBCS[14].

Genetic Data

DNA was extracted from either whole blood or mouthwash samples (n=345). Genotyping was completed for 933 women from the 4-CBCS who self-identified as NHW, 412 Hispanic, 8 NA, 14 NHW/Hispanic, 10 NHW/NA, 10 Hispanic/NA, and 4 NHW/Hispanic/NA and for 252 women from the SFBCS who self-reported being NHW and 694 who reported being Hispanic. A tagSNP approach was used to characterize variation across candidate genes. TagSNPs were selected 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 of -1500 bps from the initiation codon to +1500 bps from the termination codon; and 1 SNP/LD bin. We used 104 Ancestry Informative Markers (AIMs) to distinguish European and Native American (NA) ancestry in the study population[8]. All markers were genotyped using a multiplexed bead array assay format based on GoldenGate chemistry (Illumina, San Diego, California). The following genes were evaluated: *DUSP4* (6 SNPs), *DUSP6* (1 SNP), *MAP2K1* (6 SNPs), *MAP3K1* (7 SNPs), *MAP3K2* (3 SNPs), *MAP3K3* (2 SNPs), *MAP3K7* (6 SNPs), *MAP3K9* (19 SNPs), *MAPK1* (6 SNPs), *MAPK3* (1 SNP), *MAPK8* (4 SNPs), *MAPK12* (2 SNPs), and *MAPK14* (9 SNPs).

Tumor Characteristics and Survival

Data on survival were available from state cancer registries and included date of death or last follow-up (month and year), cause of death, and stage of disease at time of diagnosis. Survival (in months) was calculated as the difference between diagnosis date and date of death or last follow-up. Survival data in this report includes survival through December 2011 for Utah, Colorado, and California, through 2010 for Arizona, and through 2008 for New Mexico.

Statistical Methods

The program STRUCTURE was used to compute individual ancestry for each study participant assuming two founding populations[15, 16]. Participants were classified by level of percent NA genetic ancestry. Assessment across categories of ancestry was done using cut-points based on the distribution of genetic ancestry in the control population with the goal of creating distinct ancestry groups that had sufficient power to assess associations. Two strata of ≤28% and >28% were used to evaluate associations by level of NA ancestry since a two population structure best fit the population.

Associations between SNPs and diet and lifestyle factors and all-cause mortality and breast cancer-specific mortality were evaluated using Cox proportional hazards models to obtain multivariate hazard ratios (HR) and 95% confidence intervals (CI) for all women and within strata of genetic ancestry using SAS version 9.3 (SAS Institute, Cary, NC). Individuals were censored if they were lost to follow-up. When examining breast cancer-specific mortality, women who died of other causes also were censored. All SNPs were evaluated as a co-dominant model and if initial analysis suggested too few homozygote variants a dominant model was used. In other instances where a recessive model appeared to fit the data, it was used to evaluate risk estimates. Models were adjusted for age, study center, BMI (continuous), percent NA ancestry (continuous), and SEER stage (local, regional, distant).

We used the adaptive rank truncated product (ARTP) method that utilizes a highly efficient permutation algorithm to determine the significance of each gene and of the overall pathway with survival[17, 18]. We permuted the survival outcome 10,000 times in R version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria). SNP associations were assessed among the observed and permuted data in R using p values from likelihood-ratio tests comparing Cox proportional hazards models with and without the SNP variable. The P_{ARTP} is based on assessment of five truncation points for the pathway and each gene. Results included in tables are based on SNPs that had significant ($p<0.05$) or marginally significant (0.07 or less) gene p values and/or SNPs that were statistically different by ancestry group.

Interactions between genetic variants and lifestyle factors, including cigarette smoking (ever vs never), any alcohol consumption during lifetime (any vs none), a history of diabetes (yes vs no), and dietary factors during referent year (quartiles of nutrient consumption/1000 calories categorized by study-specific control distribution with data presented with middle two quartiles combined) were assessed using p values from one-degree of freedom Wald chi-square tests. We adjusted for multiple comparisons within each gene to determine significance of interactions. We used a step-down Bonferroni correction (i.e., Holm method) to adjust for multiple comparisons and utilized SNP spectral decomposition to take into account the correlated nature of the data[19, 20].

Results

Approximately the same percentage of women who self-reported being NHW and Hispanic/NA died during follow-up (Table 1). Breast cancer was the most common cause of death among NHW (48.9%) and Hispanic/NA (55.3%) women. All cancers contributed to

nearly 2/3 of deaths among NHW (64.4%) and 64.8% of deaths among Hispanic/NA women. Lung and pancreatic cancer were the next most common cancer deaths after breast cancer. Cardiovascular diseases accounted for roughly 10.5% of deaths, while respiratory diseases accounted for slightly over 4% of deaths.

Greater age, advanced SEER disease stage, a history of diabetes or high blood sugar, and lower vitamin C intake were associated with decreased survival among both NHW and Hispanic/NA women (Table 2). A history of cigarette smoking and a larger BMI were associated with poorer survival among NHW women, while being pre-menopausal, and both greater amount of long-term alcohol and any long-term alcohol consumption were associated with poorer survival among Hispanic/NA women.

Several MAPK genes were associated with breast cancer-specific mortality among women with low NA ancestry (Table 3). Although the overall pathway was not statistically significant (P_{ARTP}=0.10), *MAP2K1* (P_{ARTP}=0.04), *MAP3K9* (P_{ARTP}=0.02), and *MAPK12* (P_{ARTP}=0.05) were significantly associated with breast cancer-specific mortality and *MAPK1* was marginally significant (P_{ARTP}=0.07). Several SNPs were significantly different by ancestry (p<0.05), including *MAP3K1* rs16886403 ($HR_{TC/CC}$ for low NA ancestry = 1.48 95%CI 1.01,2.17 and for high NA =0.74 95% CI 0.45,1.19) and *MAPK1* rs9610375 (HR_{TT}= 0.56 95% CI 0.34-0.94 for low NA ancestry and HR 1.13 95% CI 0.59,2.15 for high NA ancestry) that showed stronger associations with breast cancer-specific mortality among women with low NA ancestry; *MAP3K3* rs3785574 had a stronger direct association among women with higher NA ancestry.

Stronger associations were observed between *MAPK* genes and all-cause mortality (Table 4), which also were predominately among women with low NA ancestry. The overall pathway was statistically significant among women with lower NA ancestry (P_{ARTP}=0.02). At the gene level, *MAP2K1* (P_{ARTP}=0.02), *MAP3K1* (P_{ARTP}=0.02), *MAP3K9* (P_{ARTP}=0.01), and *MAPK1* (P_{ARTP}=0.05) were associated with all-cause mortality. *MAP3K2* was significantly associated with all-cause mortality among women with higher NA ancestry (P_{ARTP}=0.04). Significant differences for all-cause mortality by NA ancestry were also noted for several SNPs in *MAP2K1* (rs1432442) (HR_{AA} 2.93 95% DI 1.46,5.87 for high NA ancestry) and *MAP3K9* where rs11625206 was significantly inversely associated with mortality among women with high NA ancestry while rs118447474, rs8010714, and rs11158881 were inversely associated with mortality among women with low NA ancestry.

Several demographic, diet, and lifestyle factors were associated with all-cause mortality and breast cancer-specific mortality (Table 5). Moderate alcohol consumption was significantly associated with lower risk of all-cause mortality. Women diagnosed when they were post-menopausal were less likely to die than women diagnosed when pre-menopausal. Histories of cigarette smoking and diabetes were both significantly associated with increased risk of all-cause mortality although the association with breast cancer-specific mortality did not reach statistical significance. High total caloric intake was associated with increased risk of both all-cause mortality and breast cancer-specific mortality, whereas high intakes of dietary folate, vitamin C, and beta carotene were associated with lower of all-cause mortality.

Assessment of interaction between diet and lifestyle factors and *MAPK* genes showed significant interaction between *DUSP4* and alcohol consumption (increased risk for rs12540995 and rs3824133 and decreased risk for rs47482 with less common genotype and low level of consumption), calories (increased risk with high caloric consumption relative to common genotype with low caloric consumption), dietary fat (both common genotype and high fat and rare genotype and low fat increased risk) and fiber (common genotype and high fiber reduced risk), and cigarette smoking (common genotype and smoking increased risk) for all-cause mortality (Table 6). *MAP3K2*, *MAP3K3*, *MAP3K7*, *MAPK1*, and *MAPK14* interacted with alcohol consumption where a pattern of the more common genotype with high alcohol consumption reduced risk of all-cause mortality. Additionally *MAPK14* interacted with calories (high intake with common genotype increased risk), dietary fiber (common genotype and high fiber reduced risk), and folate (common genotype and high folate reduced risk); *MAP3K2* interacted with diabetes (less common genotype and having diabetes increased risk); and *MAP3K7* interacted with vitamin C (no protective effect for the common genotype with low vitamin C while there was a protective effect for low vitamin C with the less common genotype).

Discussion

Several *MAPK* genes were associated with breast cancer-specific and all-cause mortality. Associations were consistently observed among women with low NA ancestry. Diet and lifestyle factors were associated with survival after adjusting for disease stage regardless of genetic ancestry. Furthermore, diet and lifestyle factors interacted with select genes in the *MAPK* pathway to alter associations with all-cause mortality.

Activation of MAPK, including ERK1/2, JNK, and p38, in breast carcinoma has been shown to induce gene expression leading to increased proliferation, invasion and metastasis [5-7]. Most studies have focused on expression of MAPK in tissue and correlations with survival and prognosis. Activated p38 (MAPK14) has been associated with poorer survival after diagnosis with breast cancer [7]. MAPK1 and MAPK3 (alias p41 and p44 in ERK pathway) expression in breast tumors also has been associated with disease-free survival[21]. Genetic variation in *MAPK* genes has not been evaluated with survival after breast cancer diagnosis, although biological plausibility for associations exists. Genes in the ERK and JNK pathways were most frequently associated with survival in our study and associations were stronger for women with low NA ancestry. It is possible that women with lower NA ancestry are exposed to a wider range of environmental stress that may activate these pathways, or that they have a genetic profile that alters expression of other genes activated by this pathway. The only gene associated with higher NA ancestry, *MAP3K2* (in the ERK pathway) also interacted with a history of diabetes. It is of interest to note that Native American women have high rates of diabetes, which could provide support for this association for both factors.

Since the majority of women included in this study were diagnosed at the local or regional disease stage, assessment of factors that may influence survival is important for clinical recommendations and possible interventions. Other studies have evaluated associations between alcohol and diet and risk of dying from breast cancer and other causes[22, 23]. Diet quality indices were not associated with breast cancer survival in a study of postmenopausal

women[24]. Alcohol was not associated with all-cause mortality, but was associated with breast cancer-specific mortality in a cohort of 1,897 women diagnosed at an early-stage breast cancer[23]. Although we observed a slight inverse association for low consumption of alcohol for all-cause mortality, there was no association for breast cancer-specific mortality. This could be the result of low levels of alcohol consumption in our study population. However, the California Breast Cancer Survivorship Consortium, which included over 2000 Latina women observed similar associations between alcohol consumption and all-cause mortality (HR 0.88) [25] as we did. The associations we observed for dietary factors are most similar to those reported by Kwan [22]. While Kwan evaluated dietary patterns and observed an inverse association with a prudent diet and an increased risk of dying with a Western diet, we observed inverse associations between vitamin C, folate, and beta carotene, and direct associations with all-cause mortality for total caloric intake.

An important component of this study is our assessment of the interaction between genes and diet and lifestyle. To maximize power, we assessed all-cause mortality for all women combined. We observed several associations, suggesting that diet and lifestyle factors can further influence survival by modifying risk associated with genetic factors. *DUSP4* and *MAPK14* (also known as p38) interacted with alcohol, calories, fat, fiber, folate, and cigarette smoking to alter survival; however neither of these genes displayed an independent association with survival. Unfortunately we were not able to look at these interactions by genetic ancestry groups, which could have revealed other unique interactions.

This study represents one of the largest studies to date to report on survival among Hispanic/NA women; however, there is not a similar population available for validation of our findings. Because our population of NA women was restricted to those not living on reservations and included few NA women, we were unable to evaluate these two groups of women separately. However to obtain a better understanding of the associations with NA ancestry, we assessed associations by genetic ancestry. Based on 104 ancestry informative markers, we were able to classify ancestry among all subjects. We have extensive genetic and lifestyle data to assess associations with survival, although some exposures such as alcohol were rare in the study population. Although we were able to assess associations with all-cause and breast cancer mortality, our analysis of all-cause mortality was more robust given the larger sample size. We focused on a unique genetic pathway relevant for breast cancer survival; however, other genes or SNPs within the pathway could also be important predictors of mortality. A limitation is the general unknown functionality of these tagging SNPs. While we have information on disease stage for women, we lack detailed information on complete treatment, although we believe that adjustment for disease stage may help overcome this limitation if women diagnosed at a similar stage and tumor type would receive similar treatment. However, we are unable to evaluate associations by type of treatment, which could be informative. As a whole, we believe that this is a unique and informative population, warranting replication.

Our study supports an association between MAPK genes and survival after diagnosis with breast cancer, with the strongest associations found among women with low NA ancestry. Diet and lifestyle factors importantly modified risk associated with these genes as well as being associated with survival independently. The interaction between genetic variation in

the *MAPK* pathway with diet and lifestyle factors supports the important role of diet and lifestyle on breast cancer survivorship

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Table 1

Causes of death of invasive breast cancer cases

		Non-Hispanic White		Hispanic/Native American	
Vital Status		**N (%)**	**Min, Max Survival Mo.**	**N (%)**	**Min, Max Survival Mo.**
	Deceased	233 (19.6)	13, 178	219 (19.0)	11, 169
	Alive[1]	953 (80.4)	1, 185	936 (81.0)	4, 185
Cause of Death					
Cancer	Breast	114 (48.9)	13, 157	121 (55.3)	11, 154
	Lung	9 (3.9)	28, 155	4 (1.8)	69, 121
	Pancreas	5 (2.1)	49, 148	3 (1.4)	46, 123
	Leukemia	5 (2.1)	24, 83	2 (0.9)	76, 160
	Colorectal	3 (1.3)	82, 123	3 (1.4)	58, 112
	Non-Hodgkins Lymphoma	2 (0.9)	104, 117	2 (0.9)	86, 120
	Stomach	2 (0.9)	100, 112	0	
	Liver	1 (0.4)	33	1 (0.5)	50
	Kidney	2 (0.9)	33, 99	0	
	Other cancer[2]	4 (1.7)	19, 157	3 (1.4)	45, 134
	Unspecified or multiple sites	3 (1.3)	49, 88	3 (1.4)	38, 133
Cardiovascular Diseases	Rheumatic Heart Disease	1 (0.4)	99	1 (0.5)	87
	Hypertensive	1 (0.4)	68	2 (0.9)	88, 115
	Ischaemic Heart Disease	7 (3.0)	37, 136	8 (3.7)	39, 134
	Pulmonary	2 (0.9)	48, 102	1 (0.5)	78
	Endocardium/cardiomyopathy, Cardiac arrest	7 (3.0)	25, 152	4 (1.8)	54, 115
	Stroke	5 (2.1)	31, 100	6 (2.7)	21, 138
	Other diseases of arteries	2 (0.9)	48, 91	1 (0.5)	62
Bacterial/viral infections		1 (0.4)	125	2 (0.9)	36, 104
Renal disease		2 (0.9)	108, 113	3 (1.4)	82, 110
Accidents including suicide		3 (1.3)	64, 141	3 (1.4)	14, 62
Other diseases of liver, intestine, connective tissue		0		9 (4.1)	29, 115
Diabetes		3 (1.3)	41, 81	4 (1.8)	31, 94
Dementia and diseases of nervous system		6 (2.6)	99, 165	4 (1.8)	82, 120

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	Non-Hispanic White		Hispanic/Native American	
Vital Status	**N (%)**	**Min, Max Survival Mo.**	**N (%)**	**Min, Max Survival Mo.**
Pneumonia	2 (0.9)	79, 127	3 (1.4)	15, 72
Other respiratory diseases	11 (4.7)	31, 114	9 (4.1)	26, 140
Unknown or ill-defined[3]	30 (12.9)	23, 178	17 (7.8)	29, 169

[1] Vital status is through December 2011 for Utah, Colorado and California, through 2010 for Arizona and through 2008 For New Mexico; includes those lost to follow-up.

[2] Includes one cancer each of palate, other and ill-defined digestive organs, larynx, cervix, uterus, ovary, and brain.

[3] Death certificate/listing unavailable, underlying death not coded, ill-defined or unknown causes, or benign neoplasm of skin.

Table 2

Description of the demographics, diet and lifestyle factors among breast cancer cases by self-reported race/ethnicity

	Non-Hispanic White			Hispanic/Native American		
	Deceased	Alive[1]	Log-Rank	Deceased	Alive[1]	Log-Rank
	N (%)	N (%)	P Value	N (%)	N (%)	P Value
Study Site						
4CBCS	155 (17)	778 (83)	0.40	66 (14)	392 (86)	0.40
SFBCS	78 (31)	176 (69)		153 (22)	544 (78)	
Age (years)						
<40	16 (21)	62 (79)	<.01	16 (16)	84 (84)	<.01
40-49	46 (14)	276 (86)		49 (13)	331 (87)	
50-59	47 (14)	284 (86)		62 (19)	260 (81)	
60-69	54(19)	237 (81)		51(2 1)	190 (79)	
≥70	70 (42)	95 (58)		41 (37)	71 (63)	
Estimated Native American ancestry						
0 - 28%	229 (19)	949 (81)	0.12	47 (21)	177 (79)	0.58
>28%	4 (44)	5 (56)		172 (18)	759 (82)	
SEER summary stage						
Local	135 (16)	695 (84)	<.01	92 (14)	557 (86)	<.01
Regional	84 (26)	239 (74)		111 (26)	321 (74)	
Distant	12 (80)	3 (20)		6 (67)	3 (33)	
Menopausal status						
Pre-menopausal	64 (16)	330 (84)	0.08	63 (14)	380 (86)	<.01
Post-menopausal	164 (21)	609 (79)		145 (22)	504 (78)	
Referent year BMI (kg/m^2)						
Normal (<25)	80 (15)	438 (85)	<.01	44 (16)	237 (84)	0.37
Overweight (25-29)	82 (23)	272 (77)		76 (19)	318 (81)	
Obese (>30)	71 (23)	242 (77)		99 (21)	378 (79)	
Long-term alcohol consumption[2]						
None	112 (20)	448 (80)	0.56	169 (22)	598 (78)	<.01
Light/Moderate	85 (18)	376 (82)		37 (12)	271 (88)	

	Non-Hispanic White			Hispanic/Native American		
	Deceased	**Alive[1]**	**Log-Rank**	**Deceased**	**Alive[1]**	**Log-Rank**
	N (%)	**N (%)**	**P Value**	**N (%)**	**N (%)**	**P Value**
High (>75% of drinkers)	36 (22)	130 (78)		13 (16)	67 (84)	
Any alcohol consumption						
Any	121 (19)	506 (81)	0.49	50 (13)	338 (87)	<0.01
History of cigarette smoking						
Yes	82 (19)	347 (81)	0.03	53 (18)	243 (82)	0.73
History of diabetes or high blood sugar[3]						
Yes	24 (32)	51 (68)	<0.0 1	49 (33)	99 (67)	<0.01
			Kruskal-Wallis			Kruskal-Wallis
	Median	Median	P Value	Median	Median	P Value
Dietary Intake (per 1000 kcal) during referent year						
Calories (kcal)	1906.15	1959.62	0.97	2212.62	2199.56	0.61
Total Fat (g)	39.7	38.49	0.17	36.16	37.17	0.09
Fiber (g)	10.43	10.73	0.10	10.83	11.04	0.96
Folate (mcg)	184.62	188.26	0.12	213.41	209.46	0.17
Vitamin C (mg)	71.14	78.74	0.02	59.25	69.49	0.03
Beta Carotene (mcg)	2175.79	2263.65	0.47	1706.36	1872.92	0.08

[1] Vital status is through December 2011 for Utah, Colorado and California, through December 2010 for Arizona and through December 2008 for New Mexico

[2] Alcohol consumption in referent year is used for women without information on long-term alcohol consumption

[3] Diabetes information was not collected for all study participants

Table 3

Associations between *MAPK* genes and breast cancer survival by genetic ancestry

	All women				0 - 28% Native American Ancestry				29 - 100% Native American Ancestry			
	Deaths/Person Years	**HR[2]**	**(95% CI)**	**P_{ARTP}**	**Deaths/Person Years**	**HR[2]**	**(95% CI)**	**P_{ARTP}**	**Deaths/Person Years**	**HR[2]**	**(95% CI)**	**P_{ARTP}**
Pathway P_{ARTP}				0.37				0.10				0.61
MAP2K1 (rs891848)				0.35				0.04				0.76
CC	180/16269	1.00			107/9560	1.00			73/6709	1.00		
CT/TT	55/6151	0.76	(0.56, 1.03)		31/3679	0.68	(0.45, 1.02)		24/2471	0.88	(0.55, 1.41)	
MAP2K1 (rs1432442)												
GG	192/17420	1.00			128/11103	1.00			64/6317	1.00		
GA	33/4752	0.63	(0.43, 0.91)		8/2079	0.36	(0.17, 0.73)		25/2674	0.87	(0.55, 1.39)	
AA	10/248	4.19	(2.17, 8.08)		2/58	3.58	(0.87, 14.79)		8/190	4.77	(2.21, 10.28)	
MAP3K1 (rs16886403)[1]				0.77				0.29				0.50
TT	176/17096	1.00			101/10429	1.00			75/6666	1.00		
TC/CC	59/5324	1.11	(0.83, 1.50)		37/2810	1.48	(1.01, 2.17)		22/2514	0.74	(0.45, 1.19)	
MAP3K3 (rs3785574)[1]				0.52				0.61				0.09
AA	105/10074	1.00			69/6130	1.00			36/3944	1.00		
AG	98/9930	0.89	(0.68, 1.18)		55/5829	0.76	(0.53, 1.08)		43/4101	1.15	(0.74, 1.80)	
GG	32/2415	1.37	(0.92, 2.04)		14/1281	1.01	(0.56, 1.81)		18/1135	2.02	(1.13, 3.59)	
MAP3K9 (rs11625206)				0.03				0.02				0.81
CC	93/10416	1.00			52/5891	1.00			41/4524	1.00		
CT/TT	142/12004	1.33	(1.03, 1.74)		86/7348	1.42	(1.00, 2.01)		56/4656	1.28	(0.85, 1.92)	
MAP3K9 (rs11844774)												
TT	77/6572	1.00			53/4150	1.00			24/2422	1.00		
TC	120/11328	0.89	(0.67, 1.19)		66/6742	0.72	(0.50, 1.04)		54/4585	1.22	(0.75, 1.99)	
CC	38/4513	0.71	(0.48, 1.05)		19/2340	0.57	(0.34, 0.97)		19/2173	0.93	(0.51, 1.71)	
MAP3K9 (rs8010714)												
CC	75/6425	1.00			52/4104	1.00			23/2320	1.00		
CG	122/11369	0.92	(0.69, 1.22)		67/6758	0.75	(0.52, 1.07)		55/4611	1.27	(0.77, 2.08)	
GG	38/4626	**0.70**	(0.47, 1.03)		19/2377	0.56	(0.33, 0.95)		19/2249	0.93	(0.50, 1.72)	

	All women				0 - 28% Native American Ancestry				29 - 100% Native American Ancestry			
	Deaths/Person Years	**HR[2]**	**(95% CI)**	**P_{ARTP}**	**Deaths/Person Years**	**HR[2]**	**(95% CI)**	**P_{ARTP}**	**Deaths/Person Years**	**HR[2]**	**(95% CI)**	**P_{ARTP}**
MAP3K9 (rs11628333)												
TT	81/9267	1.00			48/5488	1.00			33/3778	1.00		
TC/CC	154/13140	1.38	(1.05, 1.81)		90/7738	1.42	(1.00, 2.02)		64/5402	1.38	(0.91, 2.11)	
MAP3K9 (rs11622989)												
CC/CT	191/17145	1.00			116/10126	1.00			75/7019	1.00		
TT	44/5275	0.68	(0.49, 0.95)		22/3114	0.55	(0.35, 0.88)		22/2161	0.86	(0.53, 1.38)	
MAP3K9 (rs12883244)												
CC/CT	190/16583	1.00			115/9729	1.00			75/6855	1.00		
TT	45/5837	0.65	(0.47, 0.90)		23/3511	0.53	(0.34, 0.83)		22/2326	0.82	(0.51, 1.32)	
MAP3K9 (rs8022269)												
GG	66/7800	1.00			34/4588	1.00			32/3212	1.00		
GA/AA	169/14610	1.41	(1.06, 1.87)		104/8651	1.66	(1.13, 2.46)		65/5958	1.16	(0.76, 1.78)	
MAP3K9 (rs11624934)												
AA	87/10260	1.00			51/6306	1.00			36/3953	1.00		
AG/GG	148/12145	1.49	(1.14, 1.94)		87/6918	1.64	(1.16, 2.33)		61/5227	1.33	(0.88, 2.02)	
MAPK1 (rs9610375)[1]				0.37				0.07				0.94
GG	88/7334	1.00			50/3585	1.00			38/3748	1.00		
GT	112/10735	0.87	(0.66, 1.15)		66/6802	0.68	(0.47, 0.99)		46/3933	1.15	(0.75, 1.78)	
TT	34/4239	0.74	(0.50, 1.11)		21/2755	0.56	(0.34, 0.94)		13/1484	1.13	(0.59, 2.15)	
MAPK1 (rs9610470)												
TT	160/14077	1.00			92/7699	1.00			68/6378	1.00		
TC/CC	75/8315	0.80	(0.61, 1.06)		46/5513	0.67	(0.47, 0.96)		29/2802	1.03	(0.67, 1.60)	
MAPK12 (rs2272857)				0.06				0.05				0.41
GG	131/11269	1.00			90/7361	1.00			41/3907	1.00		
GA/AA	69/8036	0.71	(0.53, 0.95)		40/4934	0.65	(0.45, 0.95)		29/3102	0.82	(0.51, 1.33)	

[1] Significant differences in survival by genetic ancestry group at the 0.05 level

[2] Hazard ratios (HR) and 95% confidence intervals (CI) calculated among primary invasive cases and adjusted for age, study, BMI during referent year, parity, percent Native American ancestry, and SEER summary stage.

Table 4

Associations between MAPK genes and all-cause mortality by genetic ancestry

	All Women				0 - 28% Native American Ancestry				29 - 100% Native American Ancestry			
	Deaths/Person Years	**HR[2]**	**(95% CI)**	**P_{ARTP}**	**Deaths/Person Years**	**HR[2]**	**(95% CI)**	**P_{ARTP}**	**Deaths/Person Years**	**HR[2]**	**(95% CI)**	**P_{ARTP}**
Pathway P_{ARTP}				0.55				0.02				0.50
MAP2K1 (rs891848)				0.54				0.02				0.28
CC	335/16269	1.00			207/9560	1.00			128/6709	1.00		
CT	111/5633	0.92	(0.74, 1.15)		64/3322	0.81	(0.61, 1.07)		47/2311	1.13	(0.80, 1.58)	
TT	6/518	0.43	(0.19, 0.98)		5/357	0.47	(0.19, 1.17)		1/161	0.23	(0.03, 1.65)	
MAP2K1 (rs1432442)[1]												
GG	366/17420	1.00			250/11103	1.00			116/6317	1.00		
GA	75/4752	0.75	(0.58, 0.96)		24/2079	0.53	(0.35, 0.80)		51/2674	0.99	(0.71, 1.38)	
AA	11/248	2.54	(1.38, 4.69)		2/58	1.90	(0.47, 7.72)		9/190	2.93	(1.46, 5.87)	
MAP2K1 (rs8039880)												
AA/AG	428/21495	1.00			268/12793	1.00			160/8702	1.00		
GG	23/922	1.32	(0.87, 2.01)		8/447	0.88	(0.44, 1.78)		15/475	1.77	(1.03, 3.03)	
MAP3K1 (rs16886403)				0.05				0.02				0.44
TT	332/17096	1.00			203/10429	1.00			129/6666	1.00		
TC/CC	120/5324	1.26	(1.02, 1.56)		73/2810	1.50	(1.14, 1.97)		47/2514	0.96	(0.68, 1.34)	
MAP3K1 (rs33330)												
GG	250/11556	1.00			138/5602	1.00			112/5953	1.00		
GA/AA	200/10829	0.82	(0.68, 1.00)		138/7623	0.71	(0.56, 0.90)		62/3207	1.08	(0.78, 1.48)	
MAP3K1 (rs2548663)												
AA	161/8776	1.00			125/6659	1.00			36/2117	1.00		
AG	208/9989	1.23	(0.99, 1.52)		121/5438	1.22	(0.95, 1.57)		87/4551	1.18	(0.79, 1.75)	
GG	83/3646	1.38	(1.04, 1.83)		30/1142	1.53	(1.02, 2.30)		53/2503	1.31	(0.85, 2.01)	
MAP3K2 (rs3732209)[1]				0.44				0.71				0.04
TT	275/13115	1.00			144/6900	1.00			131/6214	1.00		
TC/CC	145/8000	0.91	(0.75, 1.10)		131/6334	1.06	(0.84, 1.35)		45/2966	0.69	(0.49, 0.97)	
MAP3K2 (rs6732279)[1]												
TT	117/5167	1.00			43/2079	1.00			74/3088	1.00		

	All Women				0 - 28% Native American Ancestry				29 - 100% Native American Ancestry			
	Deaths/Person Years	**HR[2]**	**(95% CI)**	**P_{ARTP}**	**Deaths/Person Years**	**HR[2]**	**(95% CI)**	**P_{ARTP}**	**Deaths/Person Years**	**HR[2]**	**(95% CI)**	**P_{ARTP}**
TG/GG	335/17253	0.88	(0.70, 1.09)		233/11161	1.16	(0.83, 1.63)		102/6093	0.73	(0.53, 0.99)	
MAP3K9 (rs11625206)[1]				0.14				0.01				0.37
CC/CT	403/20282	1.00			235/11786	1.00			168/8497	1.00		
TT	49/2137	1.14	(0.85, 1.54)		41/1454	1.42	(1.02, 1.98)		8/684	0.59	(0.29, 1.21)	
MAP3K9 (rs11844774)[1]												
TT	146/6572	1.00			106/4150	1.00			40/2422	1.00		
TC/CC	305/15841	0.85	(0.69, 1.03)		169/9083	0.71	(0.56, 0.91)		136/6758	1.18	(0.83, 1.69)	
MAP3K9 (rs8010714)[1]												
CC	143/6425	1.00			104/4104	1.00			39/2320	1.00		
CG/GG	309/15995	0.85	(0.69, 1.03)		172/9135	0.72	(0.56, 0.92)		137/6860	1.17	(0.81, 1.67)	
MAP3K9 (rs12883244)												
CC	109/4744	1.00			71/2864	1.00			38/1880	1.00		
CT	244/11839	0.92	(0.73, 1.16)		149/6865	0.89	(0.67, 1.19)		95/4974	0.99	(0.68, 1.45)	
TT	99/5837	0.72	(0.55, 0.95)		56/3511	0.63	(0.44, 0.90)		43/2326	0.88	(0.56, 1.36)	
MAP3K9 (rs11158881)[1]												
TT	255/11564	1.00			178/7418	1.00			77/4146	1.00		
TC/CC	197/10815	0.81	(0.67, 0.98)		98/5780	0.70	(0.54, 0.89)		99/5035	1.05	(0.77, 1.41)	
MAP3K9 (rs4902855)												
CC	146/6639	1.00			89/4059	1.00			57/2580	1.00		
CT	233/11413	0.93	(0.76, 1.15)		148/6731	1.00	(0.77, 1.31)		85/4682	0.84	(0.60, 1.18)	
TT	73/4368	0.75	(0.57, 1.00)		39/2450	0.71	(0.49, 1.03)		34/1919	0.78	(0.51, 1.20)	
MAP3K9 (rs12590049)												
GG	268/12513	1.00			148/6848	1.00			120/5665	1.00		
GA/AA	184/9907	0.87	(0.72, 1.05)		128/6392	0.96	(0.75, 1.21)		56/3515	0.72	(0.52, 1.00)	
MAP3K9 (rs8022269)												
GG	142/7800	1.00			78/4588	1.00			64/3212	1.00		
GA/AA	310/14610	1.23	(1.00, 1.50)		198/8651	1.39	(1.07, 1.80)		112/5958	1.03	(0.75, 1.40)	
MAP3K9 (rs11624934)												
AA	194/10260	1.00			119/6306	1.00			75/3953	1.00		

	All Women				0 - 28% Native American Ancestry				29 - 100% Native American Ancestry			
	Deaths/Person Years	**HR[2]**	**(95% CI)**	**P_{ARTP}**	**Deaths/Person Years**	**HR[2]**	**(95% CI)**	**P_{ARTP}**	**Deaths/Person Years**	**HR[2]**	**(95% CI)**	**P_{ARTP}**
AG	206/9886	1.17	(0.96, 1.43)		121/5594	1.20	(0.93, 1.55)		85/4292	1.13	(0.83, 1.54)	
GG	52/2259	1.24	(0.91, 1.69)		36/1324	1.46	(1.00, 2.12)		16/935	0.92	(0.53, 1.59)	
MAPK1 (rs17759598)				0.17				0.05				0.98
TT	358/17618	1.00			208/9894	1.00			150/7724	1.00		
TC	86/4437	0.99	(0.78, 1.25)		64/3063	1.02	(0.76, 1.35)		22/1374	0.95	(0.60, 1.49)	
CC	7/362	1.08	(0.51, 2.28)		3/280	0.54	(0.17, 1.68)		4/82	3.84	(1.38, 10.64)	
MAPK1 (rs9610375)												
GG	167/7334	1.00			95/3585	1.00			72/3748	1.00		
GT	214/10735	0.88	(0.71, 1.08)		133/6802	0.75	(0.57, 0.97)		81/3933	1.08	(0.78, 1.48)	
TT	69/4239	0.76	(0.57, 1.01)		46/2755	0.65	(0.46, 0.93)		23/1484	0.98	(0.61, 1.59)	

[1] Significant differences in survival by genetic ancestry group at the 0.05 level

[2] Hazard ratios (HR) and 95% confidence intervals (CI) calculated among primary invasive cases and adjusted for age, study, BMI during referent year, parity, percent Native American ancestry, and SEER summary stage.

Table 5

Associations of lifestyle factors with survival after diagnosis with breast cancer

	All-Cause Mortality			Breast Cancer-specific Mortality		
	Deaths/Person Years	**HR[5]**	**(95% CI)**	**Deaths/Person Years**	**HR[5]**	**(95% CI)**
Long-term alcohol consumption						
None	281/12468	1.00		141/12468	1.00	
Low/Moderate	122/7579	0.77	(0.62, 0.96)	68/7579	0.88	(0.65, 1.20)
High (top 25% of drinkers)	49/2373	0.96	(0.70, 1.31)	26/2373	1.02	(0.66, 1.57)
Any alcohol consumption						
None	281/12468	1.00		141/12468	1.00	
Any	171/9952	0.82	(0.67, 1.00)	94/9952	0.92	(0.69, 1.21)
History of cigarette smoking[1]						
No	178/10011	1.00		99/10011	1.00	
Yes	135/6306	1.26	(1.01, 1.59)	67/6306	1.14	(0.83, 1.56)
History of diabetes or high blood sugar[2]						
Never diagnosed	300/17016	1.00		172/17016	1.00	
Ever diagnosed	73/1989	1.74	(1.32, 2.30)	26/1989	1.27	(0.82, 1.97)
Caloric Intake (during referent year)						
Low	106/5614	1.00		40/5614	1.00	
Moderate	218/11346	1.05	(0.83, 1.33)	116/11346	1.29	(0.89, 1.85)
High	127/5435	1.46	(1.11, 1.91)	79/5435	1.74	(1.17, 2.58)
Total fat Intake per 1000 Cal[3]						
Low	101/5552	1.00		52/5552	1.00	
Moderate	237/11263	1.17	(0.93, 1.48)	129/11263	1.23	(0.89, 1.70)
High	113/5580	1.14	(0.87, 1.50)	54/5580	1.01	(0.69, 1.48)
Dietary fiber Intake per 1000 Cal						
Low	114/5646	1.00		56/5646	1.00	
Moderate	228/11330	0.93	(0.74, 1.16)	129/11330	1.26	(0.92, 1.73)
High	109/5418	0.88	(0.67, 1.15)	50/5418	1.08	(0.73, 1.60)
Folic acid Intake per 1000 Cal[4]						

	All-Cause Mortality			Breast Cancer-specific Mortality		
	Deaths/Person Years	**HR[5]**	**(95% CI)**	**Deaths/Person Years**	**HR[5]**	**(95% CI)**
Low	118/5633	1.00		63/5633	1.00	
Moderate	239/11249	0.96	(0.77, 1.20)	131/11249	1.09	(0.80, 1.47)
High	94/5513	0.73	(0.56, 0.97)	41/5513	0.73	(0.49, 1.09)
Vitamin C intake per 1000 Cal						
Low	126/5409	1.00		66/5409	1.00	
Moderate	225/11318	0.77	(0.62, 0.96)	121/11318	0.89	(0.66, 1.20)
High	100/5668	0.70	(0.54, 0.92)	48/5668	0.74	(0.51, 1.08)
Beta carotene intake per 1000 Cal						
Low	112/5539	1.00		59/5539	1.00	
Moderate	243/11216	0.97	(0.77, 1.22)	126/11216	1.17	(0.85, 1.60)
High	96/5640	0.73	(0.55, 0.96)	50/5640	0.98	(0.67, 1.45)

[1] Includes all 4-CBCS women and SFBCS women who completed questionnaire 3 (Hispanics only)

[2] includes all 4-CBCS women and SFBCS women who completed questionnaire 2 (NHW and Hispanics) and 3 (Hispanics only).

[3] Borderline significant difference in overall mortality by genetic ancestry observed, p=0.059 where HR of 1.46 (95%CI 1.02, 2.07) observed for ≤28% NA ancestry and HR of 0.82 (95% CI 0.52, 1.29) for >28% NA ancestry.

[4] Significant difference in overall mortality by genetic ancestry observed, p=0.046 where HR of 0.56 (95%CI 0.39, 0.81) observed for ≤28% NA ancestry and HR of 1.11 (95% CI 0.69, 1.79) for >28% NA ancestry.

[5] Hazard Ratios (HR) and 95% Confidence Intervals (CI) estimates among primary invasive breast cancer cases are adjusted for age, study, BMI during referent year, parity, genetic ancestry, and SEER summary stage.

Table 6

Interaction between *MAPK* genes and diet and lifestyle factors and risk of death from any cause

	Genotype (GT)[1]		GT1/High Lifestyle		GT2/Low Lifestyle		GT2/High Lifestyle		Interaction P-value
Gene/SNP	**1 (common)**	**2 (rare)**	**HR[1]**	**(95% CI)**	**HR[1]**	**(95% CI)**	**HR[1]**	**(95% CI)**	**raw, adjusted[4]**
Alcohol (None vs. Any)									
DUSP4 (rs12540995)	CC	TT	1.02	(0.76,1.35)	**1.48**	**(1.03,2.12)**	0.62	(0.36,1.09)	0.006, 0.017
DUSP4 (rs3824133)	AA	GG	1.04	(0.78,1.39)	**1.72**	**(1.13,2.61)**	0.58	(0.29,1.15)	0.006, 0.017
DUSP4 (rs567436)	AA	TT	0.94	(0.71,1.24)	1.20	(0.84,1.73)	**0.52**	**(0.29,0.95)**	0.043, 0.044
DUSP4 (rs474824)	CC	CT/TT	**0.45**	**(0.28,0.73)**	**0.73**	**(0.54,1.00)**	0.74	(0.53,1.02)	0.003, 0.012
MAP3K2 (rs3732209)	TT	TC/CC	**0.67**	**(0.52,0.87)**	**0.76**	**(0.59,0.98)**	0.81	(0.62,1.07)	0.021, 0.054
MAP3K2 (rs6732279)	TT	TG/GG	**0.55**	**(0.36,0.84)**	**0.74**	**(0.57,0.96)**	**0.68**	**(0.51,0.91)**	0.032, 0.054
MAP3K3 (rs11658329)	GG	CC	**0.72**	**(0.55,0.94)**	**0.46**	**(0.24,0.87)**	1.10	(0.68,1.78)	0.024, 0.044
MAP3K7 (rs205342)	AA	GG	1.03	(0.77,1.38)	**1.65**	**(1.16,2.36)**	0.75	(0.43,1.28)	0.007, 0.030
MAP3K7 (rs711267)	AA	GG	**0.73**	**(0.55,0.97)**	0.65	(0.35,1.20)	**1.98**	**(1.19,3.29)**	0.004, 0.019
MAPK1 (rs743409)	CC	TT	**0.66**	**(0.46,0.96)**	0.81	(0.57,1.15)	0.99	(0.68,1.43)	0.035, 0.141
MAPK1 (rs8136867)	AA	GG	**0.65**	**(0.44,0.95)**	0.85	(0.60,1.20)	0.99	(0.68,1.45)	0.048, 0.143
MAPK14 (rs851011)	TT	TC/CC	**0.68**	**(0.54,0.86)**	0.82	(0.60,1.11)	1.13	(0.83,1.53)	0.002, 0.011
Calories									
DUSP4 (rs474824)	CC	CT/TT	**2.69**	**(1.48,4.89)**	1.28	(0.72,2.20)	**1.73**	**(1.00,2.99)**	0.019, 0.076
MAPK14 (rs3730327)	AA	AG/GG	**1.71**	**(1.27,2.30)**	1.44	(0.93,2.25)	0.99	(0.55,1.76)	0.008, 0.050
MAPK14 (rs7761118)	GG	GA/AA	**1.70**	**(1.20.2.29)**	1.51	(0.96,2.38)	0.95	(0.51,1.72)	0.005, 0.035
Fat									
DUSP4 (rs12540995)	CC	TT	**1.52**	**(1.00,2.31)**	**2.13**	**(1.25,3.62)**	1.52	(0.77,3.00)	0.039, 0.078
DUSP4 (rs3824133)	AA	GG	**1.65**	**(1.07,2.54)**	**2.91**	**(1.59,5.34)**	0.94	(0.33,2.67)	0.007, 0.027
DUSP4 (rs474824)	CC	TT	0.61	(0.32,1.15)	0.57	(0.32,1.01)	0.96	(0.56,1.62)	0.023, 0.070
Fiber									
DUSP4 (rs3824133)	AA	GG	**0.63**	**(0.41,0.95)**	0.78	(0.33,1.82)	1.32	(0.75,2.32)	0.024, 0.097
MAPK14 (rs3804454)	AA	AC/CC	**0.69**	**(0.49,0.97)**	0.79	(0.52,1.18)	1.03	(0.72,1.47)	0.021, 0.129
MAPK14 (rs17714205)	CC	CT/TT	**0.74**	**(0.55,1.00)**	**0.55**	**(0.30,1.00)**	1.07	(0.70,1.63)	0.010, 0.074
Vitamin C									
MAP3K7 (rs3799912)	AA	AG/GG	**0.62**	**(0.46,0.82)**	**0.51**	**(0.29,0.88)**	0.71	(0.44,1.14)	0.025, 0.117

Gene/SNP	Genotype (GT)[1] 1 (common)	2 (rare)	GT1/High Lifestyle HR[1]	(95% CI)	GT2/Low Lifestyle HR[1]	(95% CI)	GT2/High Lifestyle HR[1]	(95% CI)	Interaction P-value raw, adjusted[4]
Folate									
MAPK14 (rs3804454)	AA	AC/CC	**0.57**	**(0.40,0.81)**	0.68	(0.45,1.02)	0.78	(0.54,1.12)	0.021, 0.127
MAPK14 (rs17714205)	CC	CT/TT	**0.63**	**(0.46,0.86)**	**0.52**	**(0.29,0.95)**	0.82	(0.53,1.29)	0.025, 0.128
MAPK14 (rs851006)	GG	GA/AA	**0.55**	**(0.38,0.79)**	0.75	(0.52,1.10)	0.83	(0.57,1.21)	0.012, 0.083
Smoking[2]									
DUSP4 (rs12540995)	CC	TT	**1.58**	**(1.14,2.19)**	1.37	(0.87,2.16)	1.11	(0.62,1.97)	0.038, 0.042
DUSP4 (rs3824133)	AA	GG	**1.66**	**(1.19,2.31)**	**1.74**	**(1.03,2.95)**	0.93	(0.43,2.04)	0.007, 0.027
DUSP4 (rs567436)	AA	TT	**1.60**	**(1.16,2.20)**	1.21	(0.78,1.88)	0.82	(0.42,1.60)	0.015, 0.042
MAP3K2 (rs6732279)	TT	TG/TT	0.81	(0.52,1.27)	**0.65**	**(0.47,0.90)**	0.97	(0.69,1.35)	0.023, 0.061
MAPK12 (rs742184)	CC	TT	**1.45**	**(1.02,2.07)**	1.40	(0.82,2.38)	0.37	(0.13,1.01)	0.030, 0.059
Diabetes or high blood sugar diagnosis[3]									
MAP3K2 (rs12613413)	TT	CC	**1.51**	**(1.08,2.10)**	**0.34**	**(0.14,0.82)**	**4.29**	**(1.04,17.65)**	0.010, 0.026

[1] Hazard ratio (HR) and 95% confidence intervals (CI) for all cause-mortality among primary invasive cases; adjusted for age, study, BMI during referent year, parity, percent Native American ancestry, and SEER summary stage and high or low lifestyle factor. Referent group for interactions is Genotype group (GT)1 (homozygous common genotype and low lifestyle factor). Significant findings in bold text.

[2] Smoking includes all 4-CBCS women and SFBCS women who completed questionnaire 3 (Hispanics only)

[3] Diabetes diagnosis includes all 4-CBCS women and SFBCS women who completed questionnaire 2 (NHW and Hispanics) and 3 (Hispanics only)

[4] Adjusted for multiple comparisons as described in methods