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Energy homeostasis genes and survival after breast cancer diagnosis: The Breast Cancer Health Disparities Study

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Abstract

Purpose—The leptin-signaling pathway and other genes involved with energy homeostasis (EH), have been examined in relation to breast cancer risk as well as to obesity. We test the hypothesis that genetic variation in EH genes influences survival after diagnosis with breast cancer and that body mass index (BMI) will modify that risk.

Methods—We evaluated associations between 10 energy homeostasis genes and survival among 1186 non-Hispanic white (NHW) and 1155 Hispanic/Native American women diagnosed with breast cancer. 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—The overall EH pathway was marginally significant for all-cause mortality among women with low NA ancestry (P_{ARTP} = 0.057). Within the pathway, ghrelin (*GHRL*) and leptin receptor (*LEPR*) were significantly associated with all-cause mortality (P_{ARTP} = 0.035 and 0.007, respectively). The EH pathway was significantly associated with breast cancer-specific mortality among women with low NA ancestry (P_{ARTP} = 0.038). Three genes, cholecystokinin (*CCK*), *GHRL*, and *LEPR* were significantly associated with breast cancer-specific mortality among women with low NA ancestry (P_{ARTP} = 0.046, 0.015, and 0.046, respectively) while neuropeptide Y (*NPY*) was significantly associated with breast cancer-specific mortality among women with higher NA ancestry (P_{ARTP} = 0.038). BMI did not modify these associations.

Conclusions—Our data support our hypothesis that certain EH genes influence survival after diagnosis with breast cancer; associations appear to be most important among women with low NA ancestry.

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Keywords

Breast Cancer; Energy Homeostasis; Leptin Receptor; Ghrelin; Nueropeptide Y; cholecystokinin

The leptin-signaling pathway is positively associated with obesity and has been shown to stimulate the growth of human breast cancer cells. The biological effects of leptin (LEP) are exerted through binding to the leptin receptor (LEPR). This receptor is expressed in a variety of immune cells and has been shown in breast cancer cell lines to have direct communication with estrogen receptor alpha (1). The leptin-signaling pathway, along with other energy homeostasis (EH) genes, have been examined in relation to breast cancer risk as well as to obesity (2). Cocaine and amphetamine regulated transcript protein (*CARTPT*), cholecystokinin (*CCK*), leptin (*LEP*), leptin receptor (*LEPR*), Membrane Bound O-Acyltransferase Domain Containing 4 (*MBOAT4*), melanocortin 4 receptor (*MC4R*), neuropeptide Y (*NPY*), and proopiomelanocortin (POMC) ghrelin/obestatin prepropeptide (*GHRL*), are neuropeptides involved in the regulation of appetite and satiety. Ghrelin/obestatin prepropeptide (*GHRL*) is involved in energy homeostasis and regulation of body weight through its influence on satiety. Polymorphisms in *GHRL* have been linked to breast cancer risk as well as to obesity and insulin levels (3). *GHRL* Membrane Bound O-Acyltransferase Domain Containing 4 (*MBOAT4*) codes the ghrelin O-acyltransferase (GOAT) enzyme that acrylates ghrelin to enable its endocrine actions(4).

While studies have examined the relationship between EH genes with breast cancer risk, there is rationale for their involvement in survival after diagnosis with breast cancer. Variants in *LEP* and *LEPR* have been associated with breast cancer-specific mortality (5). Given the role of EH genes in maintaining body weight, serum levels of adiponectin have been associated with insulin resistance and differences in adipokines such as adiponectin levels have been associated with survival (6). LEP, NPY, and GHRL levels have been shown to regulate growth hormone secretion and promote cell growth (7-11). LEP has been shown to have angiogenesis properties and stimulate growth of human breast cancer cells (5, 12, 13). Several neuropeptides have been hypothesized as playing a role in cachexia, or extreme weight loss or wasting after cancer diagnosis (14). Cachexia is associated with decreased survival.

In this study we examine the relationship between ten EH genes and all-cause and breast cancer-specific mortality. These genes were selected because of their association with energy homeostasis and cancer and/or obesity. We evaluate associations by genetic ancestry, given differences in risk associated with these genes by Native American (NA) ancestry (15). Additionally, NA ancestry has been shown to be an important determinate of breast cancer risk among population of mixed Caucasian and NA ancestry, with women with greater NA ancestry having lower incidence of breast cancer than women of European ancestry (16, 17) We evaluate the modifying effects of body mass index (BMI) on survival given the relationship between these genes and BMI and breast cancer (15, 18-20).

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) (17). In the 4-CBCS, participants were between 25 and 79 years of age with a histologically confirmed diagnosis of first primary invasive breast cancer (n=1391) between October 1999 and May 2004 (21) and lived in one of the four 4-Corners' states of Arizona, Colorado, New Mexico, or Utah. 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 (22, 23). All participants provided informed written consent prior to participation. This study was approved by the Institutional Review Boards for Human Subjects at the University of Utah and the Cancer Prevention Institute of California.

Data Harmonization

Data were harmonized across study-specific questionnaires (17). 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. Women who reported having a hysterectomy were considered post-menopausal. BMI (kg/m^2) was calculated based on self-reported weight during the reference year or weight measured at interview (controls only) if weight during the reference year was not available. Height was based on measured height at interview or self-reported height if the measurement was declined. Categories of BMI were normal BMI (<25.0 kg/m^2), overweight (25.0-29.9 kg/m^2), or obese (≥30 kg/m^2). Parity was defined as the number of total pregnancies.

Genetic Data

DNA was extracted from either whole blood or mouthwash samples. Genotyping was completed for 933 women from the 4-CBCS who self-identified as non-Hispanic white (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. Women who self-identified as Hispanic and/or NA were considered Hispanic/NA for the analysis. 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 based on hapmap data; minor allele frequency (MAF) >0.1; range of -1500 bps from the initiation codon to +1500 bps from the termination codon; and one SNP/LD bin. Coding and non-coding SNPs were included as were both the 5′UTR and 3′UTR areas. We used 104 Ancestry Informative Markers (AIMs) to distinguish European and NA ancestry in the study population (17). 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 *ADIPOQ* (12 SNPs), *CARTPT* (5 SNPs), *CCK* (4 SNPs), *GHRL* (8 SNPs), *LEP* (9 SNPs), *LEPR* (27 SNPs), *MBOAT4* (1 SNP), *MC4R* (3 SNPs), *NPY* (4

SNPs), and *POMC* (5 SNPs). These genes and SNPs are described in online Supplement Table 1.

Tumor Characteristics and Survival

Data on survival were available from local cancer registries through December of 2013 and included date of death or last follow-up (month and year), underlying cause of death, and SEER summary stage of disease at time of diagnosis. Disease stage was obtained from tumor registries and was coded based on complete pathological reports that included extent of disease, node involvement, and metastasis. Survival (in months) was calculated as the difference between diagnosis date and date of death or last follow-up.

Statistical Methods

The program STRUCTURE was used to compute 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 with the same level of repeatability and correlation among runs as the two-founding population model. Participants were classified by level of percent NA genetic ancestry. Women who self-reported as being NHW had a low percentage of NA 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% of NA ancestry were used to evaluate associations.

Associations between SNPs and all-cause 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 NA genetic ancestry using SAS version 9.4 (SAS Institute, Cary, NC). Individuals were censored when they were lost to follow-up or if they died of causes other than breast cancer when examining breast cancer-specific mortality. All SNPs were evaluated as a co-dominant model, and if initial analysis suggested too few homozygote variants or the dominant model appeared to fit the data then a dominant model was used. In other instances where a recessive model appeared to fit the data, it was used to evaluate HR estimates. Models were adjusted for age (five-year age categories), study center, BMI (normal, overweight, obese), percent NA ancestry (continuous), parity (categorical), and stage (local, regional, distant).

A major focus of the analysis is the use of 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 (26, 27). This enables us to focus on the significance of the gene and then if genes appear to be significant, we evaluate SNPs that contribute to the gene importance. Using ARTP, we permuted the survival 10,000 times in R version 3.1.3 (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 fully adjusted Cox proportional hazards models to reduced models excluding the SNP term. The P_{ARTP} is based on assessment of a maximum of five truncation points for each gene and for the pathway. Results included in tables are based on statistically

significant genes from ARTP analysis (p of 0.05 or less) and statistically significant SNPs (p 0.05 or less) that contributed to significant gene p values.

Tests for interaction by ancestry and BMI were calculated using a Wald one degree of freedom (1-df) test; adjustments for multiple comparisons within the gene used the step-down Bonferroni correction, taking into account the correlated nature of the data using the SNP spectral decomposition method proposed by Nyholt (28) and modified by Li and Ji (29).

Results

Approximately the same percentage of women who had low NA ancestry or high NA ancestry died during follow-up (Table 1). Breast cancer was the most common cause of death among women with low NA ancestry (48.9%) and women with high NA ancestry (55.3%) women.

The age, study, menopausal status, and SEER summary stage adjusted HR for all-cause mortality for low NA ancestry versus those with high NA ancestry was 1.13 (95% CI 0.93, 1.38). Further evaluation of all-cause mortality (Table 2) showed that the overall energy homeostasis pathway evaluated was marginally significant among women with low NA ancestry (P_{ARTP} = 0.057). Within the pathway, *GHRL* and *LEPR* were significant (P_{ARTP} = 0.035 and 0.007 respectively). Two SNPs were significantly associated with *GHRL* and 11 SNPs (three in high LD in our data) were associated with *LEPR* in at least one ancestry group. Although no SNP associations were significantly different by NA ancestry after adjustment for multiple comparisons, *GHRL* rs27647 and *LEPR* rs970468, rs10749754, rs1137101, and rs6588147 were significantly different between ancestry groups prior to adjustment for multiple comparisons. Associations did not differ by level of BMI during referent year (data not shown).

Breast cancer-specific mortality HR adjusted for age, study, menopausal status and SEER summary stage for lower NA ancestry relative to higher NA ancestry was 1.15 (95% CI 0.87,1.52). Although findings associated with energy homeostasis genes were similar for breast cancer-specific mortality as was noted for all-cause mortality, associations were slightly stronger and involved more genes in the pathway (Table 3). The overall pathway was significantly associated with breast cancer-specific mortality among women with low NA ancestry. Three genes, *CCK*, *GHRL*, and *LEPR* were significantly associated with breast cancer-specific mortality among women with low NA ancestry (P_{ARTP} = 0.046, 0.015, and 0.046 respectively) and *NPY* was significantly associated with breast cancer-specific mortality among women with higher NA ancestry (P_{ARTP} = 0.038). SNPs within these genes that were associated with increased likelihood of dying comparing the rare to more common homozygote variants (*CCK* rs747455, *GHRL* rs35683, rs35682, and rs27647, *LEPR* rs970468, rsrs11585329, rs6588147, and *NPY* rs16129) and better survival with similar comparisons (*LEPR* rs7526141, rs17412175, rs6704167). Associations did not differ by level of BMI during the referent year (data not shown).

Discussion

Our study provides support for an association between EH genes and survival after diagnosis with breast cancer. *GHRL* and *LEPR* appeared to have the greatest influence for both all-cause mortality and breast cancer-specific mortality, with the strongest associations among women with low NA ancestry. *CCK* influenced breast cancer-specific mortality among women with low NA ancestry while *NPY* influenced breast cancer-specific mortality among women with higher NA ancestry. BMI did not appear to modify these associations.

Multiple *GHRL* SNPs showed significant associations with breast cancer-specific mortality. GHRL is a pleiotropic hormone predominately produced in the stomach, and is an endogenous ligand for the Growth Hormone Secretagogue Receptor (GHSR) with two major functions: the stimulation of growth hormone (GH) production and the stimulation of food intake (3). GHRL stimulates the production of GH through the activation of GHSR-1a in the hypothalamus and increases appetite and food intake independent of GHSR. In addition to its orexigenic function, GHRL also functions in cell proliferation; this function, in conjunction with the stimulatory effect on GH secretion from the anterior pituitary renders GHRL a potential factor of tumorigenesis (8). Nonetheless, little evidence has thus far been produced to show an association between *GHRL* polymorphisms and survival in breast cancer patients. However, *GHRL* polymorphisms have been associated with obesity (3) and recent studies have associated obesity with decreased survival in breast cancer patients (30, 31), particularly in Hispanics with morbid obesity (18) but these results are far from conclusive and are contradicted by other studies (32).

GHRL also plays an important role in the maintenance of the GH-IFG1 axis (3). Thus *GHRL* polymorphisms could alter hepatic IGF-1 expression levels and *IGF1* polymorphisms and expression have been associated with breast cancer survival (33, 34). Moreover, in prostate cancer GHRL is highly expressed and has been shown to initiate cross-talk to MAPK signaling cascades, playing an important role in cell proliferation via the activation of the ERK1/2 MAPK pathway, but also through an alternative p38 (MAPK14) pathway (35). While this cross-talk has yet to be shown in breast cancer tissues, both of these MAPK pathways have been associated with breast cancer survival in individuals of lower NA ancestry (36), providing a possible explanation for our observed association between *GHRL* and breast cancer survival. GHRL has also been shown to play a role in the pathophysiology of cachexia, with cachectic patients having higher GHRL concentrations, while cachexia is associated with decreased survival (14). However, other studies have shown that elevated GHRL expression is associated with increased survival in non-cachectic patients (13). Unfortunately we do not have information about how our associated SNPs affect GHRL expression.

LEPR SNPs also showed an association with breast cancer survival. LEPR is a cytokine receptor that is highly expressed in multiple tumors, including breast cancer, and in breast cancer LEPR expression is directly correlated with poor prognosis (37). LEP is predominately secreted by adipose tissue, and functions as an anorexigenic hormone responsible for appetite suppression and maintenance of EH. This control of EH is mediated via LEP induced proteolytic processing of NPY and POMC in the Arcuate nucleus of the

hypothalamus and the subsequent liberation of α-MSH; LEP also negatively regulates the orexigenic hormones NPY and Agouti Related Peptide (AgRP) (38). LEP binding to LEPR initiates multiple signal cascades to mediate its orexigenic effect, including JAK2/STAT3, phosphoinositide 3 kinase (PI3K)/Akt, and ERK MAPK, which can also promote the proliferation and survival of cancer cells (37-39). LEP signaling can also mediate anti-apoptotic effects through the overregulation of bcl-2 and expression of *survivin* and *hey2*, alter microenvironment to favor growth and progression through increases in MMP2 and E-caderine, and promote angiogenesis through VEGF and VEGFR2 (38).

Therefore LEP can act as a mitogenic, motogenic, prognostic, and angiogenic factor. LEP has also been associated with decreased survival in breast cancer patients (37, 39, 40) and with cachexia (14). While we did not duplicate these findings, we showed an association between multiple *LEPR* SNPs and breast cancer survival. Activation of LEPR leads to downstream signaling via the ERK1/2 MAPK pathway which has been associated with decreased breast cancer survival (36, 41, 42). We have previously reported that this pathway is associated with breast cancer survival in patients of low NA ancestry (36), which correlates with our findings.

CCK was associated with breast cancer-specific mortality in women of low NA ancestry. CCK is important in the control of food intake, reducing food intake and promoting satiety (43). However, CCK activation of CCK Receptor A (CCKAR) and CCK Receptor B (CCKBR) induces the chemotaxis of monocytes (44). Chronic low grade inflammation, as represented by an increased C-reactive protein (CRP), has been negatively associated with breast cancer survival (6). Moreover, CCK has been shown to function as an insulin secretagogue and islet derived CCK may act locally to prevent β cell apoptosis (45), and hyperinsulinemia is an independent risk factor for poor prognosis in women with breast cancer(6). It has been hypothesized that women with higher NA ancestry develop type 2 diabetes mellitus at a younger age and over time become hypoinsulinemic (21). If this hypothesis is correct it could explain the lower impact of *CCK* SNPs on survival in women of higher NA ancestry.

NPY rs16129 was significantly associated with survival in women of higher NA ancestry. NPY is a 36 amino acid peptide released by sympathetic nerves and is a potent trophic factor (46). In the nervous system NPY is a neurotransmitter playing a role in cognitive function, feeding behavior and cardiovascular regulation (47). NPY has been shown to increase the proliferation and migration of breast cancer cells, angiogenesis, and function in a paracrine manner to stimulate the release of cytokines, such as IL-6, IL-8, TNF-α and VEGF (46, 47). NPY Y1R, Y2R and Y5R have been reported in breast cancer lines and breast carcinomas are reported to have a high density of NPY receptors; Y5R activation stimulates growth through increased MAPK activity (7, 47, 48). This in turn leads to increased ERK 1/2 phosphorylation. Moreover, chronic stress, which is associated with breast cancer risk, leads to elevated sympathetic neurotransmitter release and sympathetics arising from the lateral and anterior cutaneous branches of the second through the sixth intercostal nerves ensure a constant supply of NPY ligands to the breast microenvironment (47). This coupled with the high density of NPY receptors may lead to a hyperactivation of the ERK1/2 MAPK system, which is associated with adverse clinical features and poor prognosis (42, 49). Poor clinical

outcome is in part due to the fact that ERK 1/2 MAPK signaling can prime estrogen receptor (ER) signaling, so that overstimulation of the system may drive ER signaling and hence tumor growth independent of an estrogen ligand (42); these hormone refractory breast cancers respond poorly to hormone ablation therapies.

Our findings show that *NPY* SNPs are associated with breast cancer-specific mortality in women of high NA ancestry. One possible explanation for this association is that chronic stress leads to elevated NPY release and that NPY is a potent chemoattractant for monocytes when acting through Y2R and Y5R (47). Moreover, NPY acts in a paracrine fashion to stimulate the release of TNF-α. We have previously shown that women of higher NA ancestry show a greater protective effect with higher intake of dietary antioxidants (50) and that *TNF* SNPs are more strongly associated with breast cancer risk and survival in women of higher NA ancestry (51).

The study has both strengths and limitations. First, we used a tagSNP approach to gather information on the genetic variation across the gene. Our tagSNP approach was implemented on a customized Illumina platform and included SNPs that were validated and considered to have a high probability of yielding results. Our tagSNPs were identified using the Illuminia data and were based mainly on Caucasian populations. While this approach allowed us to evaluate genetic variation across the gene, we may have missed important SNPs and therefore important associations. Additionally, we are limited in our knowledge of the functionality of these SNPs, which makes it difficult to determine how SNPs operate in influencing gene expression or protein levels. We were able to examine associations by NA ancestry as well as by BMI, important factors that could modify risk associated with survival. We utilized a two ancestry population since this structure best fit our data. While we had disease stage data we did not have information on treatment. We used both ARTP and Benjamin and Hochberg adjustments for multiple comparisons to identify genes and SNPs of importance for survival. However, findings could still be from chance and need replication in other ethnically diverse populations.

In summary, our results support our hypothesis that EH genes influence survival after diagnosis with breast cancer. *GRHL* and the *LEPR* appear to have the most influence on survival. *CCK* and *NPY* were associated with breast cancer-specific mortality only, while *LEPR* and *GHRL* showed associations with both all-cause and breast cancer specific mortality. The greatest influence of EH genes on survival was found among women with low NA ancestry (i.e. mostly European ancestry), although *NPY* influenced breast cancer-specific survival among women with high NA ancestry only. Body size did not appear to influence these associations with survival. Confirmation of these findings in a similar ethnically diverse population 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 Native American Ancestry

	0-28% Native American Ancestry		29-100% Native American Ancestry	
	N	%	N	%
Study Site				
4-Corners Breast Cancer Study	999	71.31	391	41.60
San Francisco Bay Area Breast Cancer Study	402	28.69	549	58.40
Age (years)				
24-39	98	7.00	80	8.51
40-49	384	27.41	317	33.72
50-59	395	28.19	258	27.45
60-69	338	24.13	194	20.64
>70	186	13.28	91	9.68
Menopausal Status				
Pre-menopausal	469	34.41	367	41.01
Post-menopausal	894	65.59	528	58.99
Self-Reported Race/Ethnicity				
non-Hispanic White	1177	84.01	9	0.96
Hispanic/Native American	224	15.99	931	99.04
Vital Status				
Deceased	297	21.20	186	19.79
Alive	1104	78.80	754	80.21
Cause of Death				
Breast Cancer	145	48.82	104	55.91
Other	152	51.2	82	44.1
SEER Summary Stage				
Local	946	69.10	532	59.91
Regional	407	29.73	348	39.19
Distant	16	1.17	8	0.90

Table 2

Associations between energy homeostasis genes and deaths from any cause by level of Native American ancestry

		Overall			0 - 28% Native American Ancestry			29 - 100% Native American Ancestry			$P_{Interaction}$ (raw, adjusted)
		Death/Person Years	HR	(95% CI)	Death/Person Years	HRR	(95% CI)	Death/Person Years	HR	(95% CI)	
Pathway P_{ARTP}			**0.414**			**0.057**			**0.713**		
***GHRL* P_{ARTP}**			**0.160**			**0.035**			**0.291**		
rs27647											0.024, 0.122
	TT	213 / 10766	1.00		94 / 5247	1.00		119 / 5519	1.00		
	TC	205 / 10410	1.03	(0.85, 1.26)	148 / 6850	1.24	(0.95, 1.61)	57 / 3560	0.80	(0.58, 1.10)	
	CC	64 / 2492	1.37	(1.03, 1.83)	55 / 2035	1.60	(1.14, 2.24)	9 / 457	0.92	(0.46, 1.83)	
rs3755777											0.271, 0.542
	GG	232 / 10669	1.00		180 / 7861	1.00		52 / 2808	1.00		
	GC/CC	249 / 13081	0.80	(0.66, 0.96)	117 / 6341	0.73	(0.58, 0.92)	132 / 6741	0.94	(0.67, 1.30)	
***LEPR* P_{ARTP}**			**0.120**			**0.007**			**0.272**		
rs7526141											0.357, 1.000
	CC	180 / 8404	1.00		92 / 3844	1		88 / 4559	1.00		
	CT	232 / 11292	0.96	(0.79, 1.17)	152 / 7438	0.83	(0.64, 1.07)	80 / 3854	1.08	(0.80, 1.47)	
	TT	71 / 4063	0.79	(0.59, 1.04)	53 / 2919	0.72	(0.51, 1.01)	18 / 1144	0.81	(0.49, 1.35)	
rs17412175[2]											0.239, 1.000
	TT	197 / 8819	1.00		107 / 4344	1.00		90 / 4475	1.00		
	TA	224 / 11368	0.89	(0.73, 1.08)	147 / 7338	0.83	(0.64, 1.06)	77 / 4029	0.93	(0.69, 1.27)	
	AA	62 / 3572	0.74	(0.56, 0.99)	43 / 2519	0.64	(0.44, 0.92)	19 / 1053	0.92	(0.56, 1.51)	
rs970468											0.007, 0.119
	TT	159 / 8358	1.00		92 / 5392	1.00		67 / 2966	1.00		
	TG	236 / 11613	1.13	(0.93, 1.39)	155 / 7041	1.40	(1.08, 1.83)	81 / 4572	0.82	(0.59, 1.13)	
	GG	88 / 3787	1.31	(1.01, 1.71)	50 / 1768	1.80	(1.26, 2.55)	38 / 2019	0.89	(0.60, 1.33)	
rs6704167[2]											0.223, 1.000
	AA	211 / 9262	1.00		118 / 4602	1.00		93 / 4660	1.00		
	AT	209 / 11106	0.81	(0.67, 0.98)	134 / 7173	0.73	(0.56, 0.93)	75 / 3933	0.89	(0.65, 1.21)	
	TT	62 / 3377	0.74	(0.55, 0.99)	44 / 2413	0.64	(0.45, 0.91)	18 / 964	0.91	(0.55, 1.51)	

		Overall			0 - 28% Native American Ancestry			29 - 100% Native American Ancestry			$P_{Interaction}$ (raw, adjusted)
		Death/Person Years	HR	(95% CI)	Death/Person Years	HRR	(95% CI)	Death/Person Years	HR	(95% CI)	
rs1171271[3]											0.065, 0.803
	TT	235 / 12400	1.00		141 / 7700	1.00		94 / 4700	1.00		
	TC	207 / 9480	1.21	(1.00, 1.46)	131 / 5682	1.31	(1.03, 1.67)	76 / 3798	1.07	(0.79, 1.45)	
	CC	41 / 1878	1.27	(0.91, 1.77)	25 / 818	1.71	(1.12, 2.64)	16 / 1060	0.87	(0.51, 1.48)	
rs1171265											0.173, 1.000
	GG	174 / 9463	1.00		105 / 5854	1.00		69 / 3609	1.00		
	GA	242 / 11186	1.19	(0.98, 1.44)	153 / 6817	1.27	(0.99, 1.62)	89 / 4368	1.07	(0.78, 1.46)	
	AA	67 / 3057	1.34	(1.01, 1.78)	39 / 1478	1.60	(1.10, 2.32)	28 / 1579	1.06	(0.68, 1.64)	
rs4370791[3]											0.175, 1.000
	AA	215 / 11463	1.00		133 / 7193	1.00		82 / 4270	1.00		
	AG	226 / 10080	1.22	(1.01, 1.47)	140 / 6062	1.28	(1.01, 1.63)	86 / 4019	1.15	(0.85, 1.56)	
	GG	42 / 2193	1.13	(0.81, 1.58)	24 / 935	1.43	(0.92, 2.22)	18 / 1258	0.86	(0.51, 1.44)	
rs10749754[4]											0.007, 0.119
	GG	140 / 7055	1.00		76 / 4368	1.00		64 / 2687	1.00		
	GA/AA	343 / 16703	1.12	(0.92, 1.37)	221 / 9833	1.42	(1.09, 1.85)	122 / 6870	0.80	(0.59, 1.09)	
rs1137101[4]											0.004, 0.073
	AA	140 / 6982	1.00		76 / 4357	1.00		64 / 2625	1.00		
	AG/GG	342 / 16667	1.09	(0.90, 1.34)	221 / 9806	1.40	(1.07, 1.82)	121 / 6861	0.77	(0.56, 1.04)	
rs11585329											0.079, 0.891
	GG	335 / 17212	1.00		194 / 10036	1.00		141 / 7176	1.00		
	GT/TT	148 / 6546	1.14	(0.94, 1.38)	103 / 4165	1.30	(1.02, 1.65)	45 / 2381	0.91	(0.65, 1.28)	
rs6588147											0.012, 0.165
	AA	186 / 9769	1.00		116 / 6382	1.00		70 / 3387	1.00		
	AG	220 / 10672	1.15	(0.94, 1.40)	136 / 6358	1.29	(1.01, 1.67)	84 / 4315	0.97	(0.70, 1.33)	
	GG	77 / 3261	1.31	(1.00, 1.72)	45 / 1406	1.85	(1.30, 2.62)	32 / 1855	0.88	(0.58, 1.34)	

[1]Hazard Ratios (HR) and 95% Confidence Intervals (CI) are adjusted for adjusted for age, study, BMI during referent year, parity, % NA ancestry, and SEER stage. Table includes of genes with ARTP $p<0.05$ and SNPs with $p<0.05$

[2]High linkage disequilibrium (LD) among women with low NA ancestry ($r^2=0.80$)

[3] High LD (r^2=0.84 among women with low NA ancestry and 0.82 among women with high NA ancestry)

[4] High LD (r^2=0.98 among women with low NA ancestry and 0.97 among women with high NA ancestry)

Table 3

Associations between energy homeostasis genes and breast cancer-specific mortality by level of Native American ancestry

		Overall			0 - 28% Native American Ancestry			29 - 100% Native American Ancestry			$P_{Interaction}$ (raw, adjusted)
		Death/Person Years	HR[1]	(95% CI)	Death/Person Years	HR	(95% CI)	Death/Person Years	HR	(95% CI)	
Pathway P_{ARTP}			**0.087**			**0.038**			**0.248**		
***CCK* P_{ARTP}**			**0.005**			**0.046**			**0.116**		
rs747455											0.949, 1.000
	GG	122 / 14043	1.00		71 / 8525	1.00		51 / 5518	1.00		
	GA/AA	127 / 9715	1.55	(1.21, 1.98)	74 / 5676	1.55	(1.12, 2.16)	53 / 4039	1.57	(1.06, 2.32)	
***GHRL* P_{ARTP}**		**0.144**				**0.015**			**0.785**		
rs35683[2]											0.051, 0.212
	CC	86 / 8265	1.00		34 / 3979	1.00		52 / 4286	1.00		
	CA	118 / 11757	1.00	(0.76, 1.33)	74 / 7425	1.25	(0.83, 1.89)	44 / 4332	0.87	(0.57, 1.30)	
	AA	45 / 3722	1.23	(0.85, 1.78)	37 / 2783	1.65	(1.03, 2.65)	8 / 939	0.73	(0.34, 1.56)	
rs35682[2]											0.035, 0.212
	AA	85 / 8043	1.00		33 / 3856	1.00		52 / 4187	1.00		
	AG	113 / 11649	0.96	(0.72, 1.28)	70 / 7271	1.20	(0.79, 1.82)	43 / 4378	0.83	(0.55, 1.26)	
	GG	51 / 4038	1.30	(0.90, 1.86)	42 / 3046	1.74	(1.09, 2.75)	9 / 992	0.77	(0.37, 1.60)	
rs27647											0.170, 0.509
	TT	107 / 10766	1.00		46 / 5247	1.00		61 / 5519	1.00		
	TC	102 / 10410	1.06	(0.80, 1.40)	66 / 6850	1.15	(0.78, 1.68)	36 / 3560	1.01	(0.66, 1.53)	
	CC	40 / 2492	1.80	(1.23, 2.63)	33 / 2035	2.18	(1.38, 3.44)	7 / 457	1.25	(0.56, 2.80)	
***LEPR* P_{ARTP}**			**0.072**			**0.046**			**0.130**		
rs7526141											0.322, 1.000
	CC	99 / 8404	1.00		49 / 3844	1.00		50 / 4559	1.00		
	CT	117 / 11292	0.91	(0.69, 1.19)	71 / 7438	0.74	(0.51, 1.08)	46 / 3854	1.10	(0.73, 1.65)	
	TT	33 / 4063	0.68	(0.45, 1.01)	25 / 2919	0.60	(0.37, 0.98)	8 / 1144	0.69	(0.33, 1.47)	
rs17412175[3]											0.432, 1.000
	TT	107 / 8819	1.00		52 / 4344	1.00		55 / 4475	1.00		

		Overall			0 - 28% Native American Ancestry			29 - 100% Native American Ancestry			$P_{Interaction}$ (raw, adjusted)
		Death/Person Years	HR[1]	(95% CI)	Death/Person Years	HR	(95% CI)	Death/Person Years	HR	(95% CI)	
	TA	113 / 11368	0.84	(0.64, 1.10)	74 / 7338	0.84	(0.59, 1.21)	39 / 4029	0.78	(0.52, 1.18)	
	AA	29 / 3572	0.64	(0.42, 0.97)	19 / 2519	0.52	(0.31, 0.90)	10 / 1053	0.87	(0.44, 1.72)	
rs970468											0.175, 1.000
	TT	78 / 8358	1.00		42 / 5392	1.00		36 / 2966	1.00		
	TG	123 / 11613	1.23	(0.92, 1.63)	81 / 7041	1.68	(1.14, 2.45)	42 / 4572	0.77	(0.49, 1.21)	
	GG	48 / 3787	1.49	(1.03, 2.15)	22 / 1768	1.77	(1.05, 3.01)	26 / 2019	1.17	(0.70, 1.95)	
rs6704167[3]											0.274, 1.000
	AA	115 / 9262	1.00		59 / 4602	1.00		56 / 4660	1.00		
	AT	103 / 11106	0.72	(0.55, 0.94)	66 / 7173	0.67	(0.47, 0.96)	37 / 3933	0.72	(0.47, 1.09)	
	TT	30 / 3377	0.67	(0.45, 1.01)	19 / 2413	0.52	(0.31, 0.88)	11 / 964	1.02	(0.53, 1.95)	
rs1171271											0.418, 1.000
	TT	112 / 12400	1.00		65 / 7700	1.00		47 / 4700	1.00		
	TC	113 / 9480	1.32	(1.02, 1.72)	67 / 5682	1.37	(0.97, 1.93)	46 / 3798	1.25	(0.83, 1.89)	
	CC	24 / 1878	1.45	(0.93, 2.26)	13 / 818	1.72	(0.94, 3.16)	11 / 1060	1.17	(0.60, 2.27)	
rs11585329											0.039, 0.681
	GG	174 / 17212	1.00		92 / 10036	1.00		82 / 7176	1.00		
	GT/TT	75 / 6546	1.15	(0.88, 1.51)	53 / 4165	1.46	(1.04, 2.05)	22 / 2381	0.79	(0.49, 1.27)	
rs6588147											0.073, 1.000
	AA	89 / 9769	1.00		52 / 6382	1.00		37 / 3387	1.00		
	AG	116 / 10672	1.23	(0.93, 1.63)	70 / 6358	1.47	(1.02, 2.12)	46 / 4315	0.95	(0.61, 1.47)	
	GG	44 / 3261	1.54	(1.06, 2.22)	23 / 1406	2.10	(1.27, 3.47)	21 / 1855	1.09	(0.64, 1.87)	
NPY **P_{ARTP}**			**0.546**			**0.365**			**0.038**		
rs16129											0.015, 0.043
	GG	73 / 8259	1.00		37 / 4048	1.00		36 / 4211	1.00		
	GT	132 / 11354	1.26	(0.94, 1.68)	83 / 7017	1.20	(0.81, 1.79)	49 / 4336	1.34	(0.86, 2.09)	
	TT	44 / 4134	1.19	(0.81, 1.74)	25 / 3124	0.82	(0.49, 1.36)	19 / 1010	2.35	(1.32, 4.19)	

[1] Hazard Ratios (HR) and 95% Confidence Intervals (CI) are for primary invasive cases; adjusted for age, study, BMI during referent year, parity, % NA ancestry, and SEER stage. Table includes genes with ARTP $p<0.05$ and SNPs with $p<0.05$

[2] High LD (r^2=0.95 among women with low NA ancestry and 0.96 among women with high NA ancestry)

[3] High LD among women with low NA ancestry (r^2=0.80)