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## Associations with growth factor genes (*FGF1*, *FGF2*, *PDGFB*, *FGFR2*, *NRG2*, *EGF*, *ERBB2*) with breast cancer risk and survival: The Breast Cancer Health Disparities Study

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### Abstract

**Background**—Growth factors (GF) stimulate cell proliferation through binding to cell membrane receptors and are thought to be involved in cancer risk and survival.

**Methods**—We examined how genetic variation in epidermal growth factor (*EGF*), neuregulin 2 (*NRG2*), *ERBB2* (HER2/neu), fibroblast growth factors 1 and 2 (*FGF1* and *FGF2*) and its receptor 2 (*FGFR2*), and platelet derived growth factor B (*PDGFB*) independently and collectively influence breast cancer risk and survival. We analyzed data from the Breast Cancer Health Disparities Study which includes Hispanic (2111 cases, 2597 controls) and non-Hispanic white (NHW) (1481 cases, 1586 controls) women. Adaptive Rank Truncated Product (ARTP) analysis was conducted to determine gene significance. Odds ratios (OR) and 95% confidence intervals were obtained from conditional logistic regression models to estimate breast cancer risk and Cox

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Proportional Hazard models were used to estimate hazard ratios (HR) of dying from breast cancer. We assessed Native American (NA) ancestry using 104 Ancestry Informative Markers.

**Results**—We observed few significant associations with breast cancer risk overall or by menopausal status other than for *FGFR2* rs2981582. This SNP was significantly associated with ER+/PR+ (OR 1.66 95% CI 1.37, 2.00) and ER+/PR- (OR 1.54 95% CI 1.03, 2.31) tumors. Multiple SNPs in *FGF1*, *FGF2*, and *NRG2* significantly interacted with multiple SNPs in *EGFR*, *ERBB2*, *FGFR2*, and *PDGFB*, suggesting that breast cancer risk is dependent on the collective effects of genetic variants in other GFs. Both *FGF1* and *ERBB2* significantly influenced overall survival, especially among women with low levels of NA ancestry ( $P_{ARTP} = 0.007$  and  $0.003$ , respectively).

**Conclusions**—Our findings suggest that genetic variants in growth factors signaling appear to influence breast cancer risk through their combined effects. Genetic variation in *ERBB2* and *FGF1* appear to be associated with survival after diagnosis with breast cancer.

### Keywords

Breast Cancer; *FGF1*; *FGFR2*; *ERBB2*; *PDGFB*; Survival; Hispanic; ER/PR

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### Introduction

Growth factors are polypeptides that stimulate cell proliferation through binding to cell membrane receptors and are thought to play an important role in the carcinogenic process [1]. Genes that encode growth factors and their receptors may be a significant subset of regulatory genes that when altered confer disease risk and influence survival. Genetic variants in several growth factor genes, such as transforming growth factor  $\beta$ , insulin-like growth factors (IGF), and vascular endothelial growth factors (VEGF) have been studied for their association with breast cancer [2-5]. Moreover, fibroblast growth factor receptor 2 (*FGFR2*) has been associated with breast cancer risk through genome wide associations studies (GWAS) exploration and subsequent replication studies [6-11].

Fibroblast growth factors (FGF1 and FGF2) are also known as heparin-binding growth factors. Fibroblasts are involved in angiogenesis, and are responsible for maintenance of extracellular matrix, regulation of epithelial cell differentiation, and regulation of inflammatory response [12]. Fibroblasts in the tumor microenvironment have been associated with tumor progression [12]. FGF1 is one of the main ligands for FGFR2. FGF2 has been associated with regulation of tumor angiogenesis and metastasis, and is positively correlated with epidermal growth factor (EGF) and IGF [13].

*EGF* and its receptor (EGFR or ERBB1) have been extensively examined with cancer risk and breast cancer specifically [14, 15]. EGFR overexpression has been correlated with loss of estrogen receptor (ER) and with poor survival [16]. While our previous work with *EGFR* has shown few genetic variants associated with breast cancer risk, it has been proposed that *EGFR* may work with other genes to modify breast cancer progression [16]. Polymorphisms of *EGF* have been examined less frequently with some studies showing associations with EGF plasma levels, but not with breast cancer risk [17]. Her2 (Neu or *ERBB2*) is structurally

similar to the EGFR and interacts with EGFR at the protein level [18]. Her2 expression has been extensively studied with breast cancer prognosis [19]; however, much less is known about genetic variants that might influence breast cancer risk or survival, although studies suggest minimal risk with rs1136201 [20]. Neuregulins (NRG) are growth and differentiation factors related to EGF; the ERBB family of tyrosine kinase transmembrane receptors are neuregulin receptors.

Platelet derived growth factor B (*PDGF*) has been shown to be a stimulator of FGF [21] and VEGF [22], leading to the conclusion that PDGF expression by tumor cells promotes angiogenesis. While it is thought that mutagenicity of one growth factor is influenced by the presence of other growth factors that collectively affect cell proliferation rates [1], PDGF has been cited as a potent mitogen that in some cells is sufficient to induce cell division in the absence of other growth factors.

In this study we examined genetic variation in seven growth-factor signaling genes, *FGF1*, *FGF2*, *FGFR2*, *NRG2*, *EGF*, *ERBB2*, and *PDGFB* in relation to breast cancer risk and survival. We utilized data from a multi-center study of breast cancer in a population of non-Hispanic white (NHW) and Hispanic women living in the United States and Mexico. We utilize 104 Ancestry Informative Markers (AIMs) to characterize the population as to their Native American (NA) ancestry since we hypothesize that differences in breast cancer risk and survival are influenced by level of NA ancestry. We evaluated associations by ER and progesterone receptor (PR), menopausal status, and family history of breast cancer.

## Methods

A case-control study design is used using data from the Breast Cancer Health Disparities Study that includes participants from three population-based case-control studies [23], the 4-Corners Breast Cancer Study (4-CBCS) [24], the Mexico Breast Cancer Study (MBCS), and the San Francisco Bay Area Breast Cancer Study (SFBCS) [25, 26] who completed an in-person interview and who had a blood or mouthwash sample available for DNA extraction. In the 4-CBCS, participants were between 25 and 79 years; participants from the MBCS were between 28 and 74 years; the SFBCS included women aged 35 to 79 years. All participants signed informed written consent prior to participation and each study was approved by the Institutional Review Board for Human Subjects at each institution.

## Data Harmonization

Data were harmonized across all study centers and questionnaires as previously described [23]. Women were classified as either pre-menopausal or post-menopausal based on responses to questions on menstrual history. Women who reported still having periods during the referent year (defined as the year before diagnosis for cases or before selection into the study for controls) were classified as pre-menopausal. Women were classified as 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). Women were categorized as having a positive family history of breast cancer if they reported having a first-degree relative with breast cancer.

## 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. 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= -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 NA ancestry in the study population [23]. All markers were genotyped using a multiplexed bead array assay format based on GoldenGate chemistry (Illumina, San Diego, California). A genotyping call rate of 99.93% was attained (99.65% for WGA samples). We included 132 blinded internal replicates representing 1.6% of the sample set. The duplicate concordance rate was 99.996% as determined by 193, 297 matching genotypes among sample pairs. In the current analysis we evaluated tagSNPs for *EGF* (1 SNP), *ERBB2* (3 SNPs), *FGF1* (21 SNPs), *FGF2* (16SNPs), *FGFR2* (1 candidate SNP), *NRG2* (22 SNPs) and *PDGFB* (9 SNPs). A description of these genes and SNPs is shown in online Supplement 1.

## Tumor Characteristics and Survival

Information on survival, differentiation, and ER/PR tumor status were not available for cases from Mexico and therefore assessment of these variables is limited to data obtained from the 4-CBCS and SFBCS. 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) summary disease stage was based on three codes of local, regional, and distant.

## Statistical Methods

### Genetic ancestry estimation

The program STRUCTURE was used to compute individual ancestry for each study participant assuming two founding populations [27, 28]. A three-founding population model was assessed but did not fit the population structure. Participants were classified by level of percent NA ancestry. Assessment across categories of ancestry was done using cut-points, 0-28%, 29-70%, and 71-100%, based on the distribution of genetic ancestry in the control population with the goal of creating distinct ancestry groups with sufficient power to assess breast cancer risk and survival.

### SNP Associations

Genes and SNPs were assessed for their association with breast cancer risk by strata of genetic ancestry and menopausal status in the whole population and by ER/PR status for the

4-CBCS and the SFBCS. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). Conditional 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 as a categorical variable and age, genetic ancestry, body mass index (BMI, kg/m<sup>2</sup>) in the reference year and parity as continuous variables. Since we observed no differences in association by *in situ* and invasive for the 4-CBCS, we include all women in the analysis of breast cancer risk. Associations with SNPs were assessed assuming a co-dominant model. Based on the initial assessment, SNPs which appeared to have a dominant or recessive mode of inheritance were evaluated with those inheritance models in subsequent analyses. For stratified analyses, tests for interactions 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 [29] and modified by Li and Ji [30]. We present findings that were statistically significant in the tables. Data were available for 7775 participants; of these 1996 women had ER/PR status and tumor characteristic data available.

### Survival Analysis

Survival months were calculated based on month and year of diagnosis and month and year of death or date of last contact by SEER registry; all cancer registry updates were through the spring of 2012. Associations between SNPs and risk of dying of breast cancer among primary invasive cases were evaluated using Cox Proportional Hazards models to obtain multivariate hazard ratios (HR) and 95% CI by admixture strata. Since survival data were not available for the MBCS study site, the upper two admixture strata were combined. Individuals were censored when they died of causes other than breast cancer or were lost to follow-up. Models were adjusted for age, study, genetic ancestry, BMI during referent year, parity, and SEER summary stage. Interactions between genetic variants and genetic ancestry with survival were assessed using p values from 1-df Wald chi-square tests.

### ARTP analysis

We used the adaptive rank truncated product (ARTP) method that utilizes a highly efficient permutation algorithm to determine the significance of association of each gene and of all genes combined with breast cancer risk overall, by menopausal status, by genetic ancestry, and by ER/PR strata. The gene p values were generated using the ARTP package in R, permuting outcome status 10,000 times while adjusting for age, reference year BMI, and genetic ancestry [31,32]. We also controlled for SEER summary stage when estimating the ARTP for survival. We report both pathway and gene p values ( $P_{\text{ARTP}}$ ). The original R program was modified to incorporate Cox Proportional Hazard modeling that permuted both vital status and survival months to estimate gene and pathway associations; p values for survival analysis were based on likelihood ratio tests.

### Results

The majority of breast cancer cases were Hispanic (62.1%), under 60 years of age (61.5%), and post-menopausal (66.5%) (Table 1). Among U.S. cases, most tumors were ER+/PR+

(68.2%). ER-/PR- tumors accounted for 18.4% of NHW and 23.4% of Hispanic cases. The majority of women who self-reported being NHW were estimated as having low NA ancestry (99.5% of controls), whereas U.S. women who self-reported being Hispanic were divided between those with intermediate NA ancestry (64.9% of controls) and high NA ancestry (24.4% of controls). Few cases were diagnosed at a distant disease stage and the majority of cases had ductal or lobular histology.

When we considered all tagSNPs in all genes together, we observed a statistically significant association between the pathway and breast cancer risk ( $P_{\text{ARTP}}$  for pathway = 0.0009). When considering the overall association between each of the genes and breast cancer risk we observed that only *FGFR2*, *PDGFB*, and *NRG2* had significant  $P_{\text{ARTP}}$  gene p values ( $P_{\text{ARTP}}$  = 0.0001, 0.045, and 0.034, respectively) based on one significant candidate SNP in *FGFR2* (rs2981582), two tagSNPs in *PDGFB* (rs9622978 and rs4821877), and four tagSNPs for *NRG2* (rs6895139, rs265155, rs1800954, and rs2436389) (Table 2). We observed no meaningful differences in associations with breast cancer risk by genetic admixture (data not shown in table) and few by menopausal status (Table 3). Associations with seven independent SNPs were significantly different by menopausal status; however of these, only *ERBB2* had a significant  $P_{\text{ARTP}}$  gene of 0.03 among post-menopausal women. Two SNPs in *FGF1* (rs4912868 and rs4912876), and one in *NRG2* (rs2436389) were associated with breast cancer risk among pre-menopausal women, although the  $P_{\text{ARTPs}}$  for these genes were not statistically significant and the magnitude of associations with these SNPs was modest. Four SNPs, *FGF1* rs9324889, *FGF2* rs308379 and rs308382, and *NRG2* rs265155 showed significant interaction with family history of breast cancer prior to adjustment for multiple comparisons, however after adjustment none of these associations remained statistically significant (see Online Supplemental Data Table 2).

When the data were analyzed within ER/PR status, associations with several SNPs were significantly different at the 0.05 level (Table 4). However, the genes for the most part were not considered significant by the  $P_{\text{ARTP}}$  as contributing to breast cancer risk within these strata. *FGFR2* was statistically significantly associated with breast cancer risk only among those with ER+ tumors. The associations of *FGF1* and *PDGFB* with ER-/PR- tumors were of borderline significance ( $P_{\text{ARTP}}$  = 0.07 and 0.08, respectively), with three *FGF1* SNPs significantly increasing risk of breast cancer and one *PDGFB* SNP associated with decreasing risk.

We examined the interaction between growth factor-related genes to determine whether the combined effect was different from the independent gene effects. We observed several significant interactions between *ERBB2* and *FGF1* and *EGFR* and *NRG2*, and between *FGFR2* rs2981582 and *FGF2* (rs7700205, rs17408757, rs1960669, and rs6534365) and *EGFR* (rs17586365 and rs6954351) (Table 5). In all instances, having both variant genotypes was associated with a greater increase in risk than having either variant genotype alone. *PDGFB* (rs9622978 and rs2247128) also interacted significantly with *FGF1* (rs250092 and rs4912868), and *PDGFB* rs6001512 interacted significantly with *FGF2* rs308435. Except for the interaction between *PDGFB* rs9622978 and *FGF1* where the homozygote common genotype of *PDGFB* and the homozygote variant of *FGF1* were associated with a significantly reduced risk compared to other genotype combinations,



having the two variant genotypes had the greatest influence on risk. *NRG2* interacted with *EGFR* (12 *NRG2* SNPs interacting with 10 *EGFR* SNPs), *FGF1* (three SNPs), *FGF2* (two SNPs), and *PDGFB* (1 SNP).

None of the growth factor-related genes seemed to influence breast cancer-specific mortality, with the exception of *ERBB2* that showed marginal associations within groups defined by genetic admixture (Table 6). However, some of these genes showed associations with all-cause mortality. Many of these associations differed by genetic admixture. Specifically, *ERBB2* rs1810132 was associated with increased the risk of both all-cause mortality ( $P_{ARTP} = 0.005$ ) and breast cancer-specific mortality ( $P_{ARTP} = 0.06$ ) among women with low NA ancestry, but was associated with decreased mortality risk among women with higher NA ancestry. Also, having a variant allele of *ERBB2* rs4252596 was associated with significantly reduced mortality risk among women with low NA ancestry, but did not influence risk among those with higher NA ancestry (heterogeneity  $p < 0.001$  for all-cause mortality and  $p = 0.003$  for breast cancer-specific mortality). *FGF1* was associated with all-cause mortality ( $P_{ARTP} = 0.04$ ), with different associations by level of NA ancestry (heterogeneity  $p = 0.03$ ). *FGF1* rs1596776 was associated with significantly increased risk of all-cause mortality among those with greater NA ancestry; *FGF1* rs17099156 was associated with increased risk of all-cause mortality among those with low NA ancestry; and *FGF1* rs152524 was associated with increased risk of breast cancer-specific mortality among those with high NA ancestry. The gene  $P_{ARTP}$  value for *FGF1* for all-cause mortality was 0.007 and the pathway  $P_{ARTP}$  was 0.005 for women with low NA ancestry.

## Discussion

In this study we studied seven genes involved in growth factor regulation that may be relevant for breast cancer development, taking into account menopausal and ER/PR status among Hispanic and NHW women stratified by level of NA ancestry. *FGFR2* and *PDGFB* were associated with breast cancer risk overall, although associations were generally modest. *ERBB2* was significantly associated with breast cancer risk among post-menopausal women only. Although no unique associations were observed by NA ancestry group, multiple associations were restricted to specific tumor subtypes. *FGFR2* was only significantly associated with breast cancer risk among those who had ER+ tumors, whereas *FGF1* was of border line significance for ER-/PR- tumors. Genetic variants in both *ERBB2* and *FGF1* were significantly associated with all-cause mortality as well as breast cancer-specific mortality among women with low NA ancestry.

Previous GWAS and replication studies have identified *FGFR2* rs2981582 as being associated with breast cancer risk [6-11]. However, few studies have evaluated this gene for associations with tumor phenotype. A study conducted in China by Cen and colleagues showed that this SNP was associated with ER+ tumors only [33]. That study also suggested that the *FGF1* rs250108 was associated with ER- tumors. The magnitudes of associations were similar to what we report here. We found that this *FGFR2* SNP is associated with all tumor types except ER-/PR- tumors, whereas *FGF1* is only associated with ER-/PR- tumors. Additionally, we show that despite associations with breast cancer risk, *FGFR2* was not associated with survival after diagnosis. However, *FGF1* influenced survival, especially

among women with low levels of NA ancestry. While FGF1 activates FGFR2, it appears that other factors may play a contributing role in terms of breast cancer risk and survival.

*ERBB2* is of interest with breast cancer risk and survival because women with *HER2* negative tumors have poorer survival than those who are *HER2* positive. Studies that have evaluated polymorphisms in *ERBB2* have often focused on rs1136201, with a large meta-analysis of 33 case-control studies showing no effect with an OR of 1.05 [20]. Conversely, another large meta-analysis of 27 published case-controls studies suggested a modest significant risk (OR 1.10 95% CI 1.01, 1.20) with stronger associations among African women. In this study we did not observe a significant associations for this SNP overall, by menopausal status, or by level of NA ancestry. However, we observed associations with survival for two other *ERBB2* SNPs (rs1810132 and rs4252596), especially among women with low levels of NA ancestry. Although associations were stronger for all-cause mortality than for breast cancer-specific mortality, given the similarities in HR estimates we believe that lack of statistical significance observed for breast cancer is due to lack of statistical power. For instance, the HRs were 0.65 (95% CI 0.40, 1.04) and 0.64 (95% CI 0.45, 0.90) for breast cancer-specific mortality and all-cause mortality respectively; we view these as comparable findings.

*PDGFB* was marginally associated with breast cancer risk overall ( $P_{ARTP}=0.049$ ), although we observed no significant associations with survival. Two SNPs also were associated with ER+/PR+ tumors and one was associated with ER-/PR- tumors. All associations were modest and the  $P_{ARTP}$  was of borderline significance for ER-/PR- tumors ( $P_{ARTP}=0.08$ ). We found no reports of association with these SNPs in other breast cancer studies. Many of the significant associations with *PDGFB* were from interaction with other growth factor genes.

It has been proposed that growth factors work together to exert their biological effect [1]. Given that hypothesis, we evaluated interaction between growth factor genes. Our data support this hypothesis, in that several genetic variants interacted to alter breast cancer risk. *FGF1* and *FGF2* illustrate this observation. *FGF1* significantly interacted with *EGFR*, *ERBB2*, and *PDGFB*, whereas *FGF2* interacted with *EGFR*, *FGFR2*, and *PDGFB*. In many instances multiple SNPs from the same gene showed interaction. For example, four SNPs in *FGF2* interacted with *FGFR2*; three SNPs in *FGF1* interacted with *PDGFB*; three SNPs in *FGF1* interacted with *EGFR*; and eight SNPs in *FGF2* interacted with *EGFR*. While we saw no significant associations of *FGF2* with breast cancer risk overall or by menopausal status, admixture, or with survival, our data suggest that *FGF2* works in conjunction with other growth factors to alter risk and may still be an important player in breast cancer carcinogenesis.

The study has many strengths including the large genetically admixed population. However, as pointed out previously, power is modest to look at breast cancer survival. This is in part because we lack survival information from MCBCS participants. We have taken a tagSNP approach to evaluate genetic variation across genes and have followed that approach by looking at the overall gene effect using ARTP statistics. Using this approach we could have missed important SNPs and associations could be chance findings. Additionally, there is



little information on the functionality of these SNPs. Thus, we encourage others to replicate these findings, especially those pertaining to survival, and to conduct functionality studies that will help guide future work in this area.

In summary, our findings suggest that associations with breast cancer risk are generally modest for the growth factors evaluated. Genetic variants in growth factor signaling appear to influence breast cancer risk through their combined effects more consistently than independent influence on risk. *FGFR2* consistently had the strongest association with breast cancer risk. However, genetic variation in *ERBB2* and *FGF1* appears to be associated with survival. These findings support the importance of considering combinatorial effects when evaluating the role of growth factors in breast cancer development and prognosis and may provide insight into treatment modalities based on an individual's genetic composition.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## References

1. Goustin AS, Leof EB, Shipley GD, Moses HL. Growth factors and cancer. *Cancer Research*. 1986; 46:1015–1029. [PubMed: 3002607]
2. Auvinen P, Lipponen P, Johansson R, Syrjänen K. Prognostic significance of TGF-beta 1 and TGF-beta 2 expressions in female breast cancer. *Anticancer research*. 1995; 15:2627–2631. [PubMed: 8669837]
3. Mu L, Katsaros D, Lu L, Preti M, Durando A, et al. TGF-beta1 genotype and phenotype in breast cancer and their associations with IGFs and patient survival. *British journal of cancer*. 2008; 99:1357–1363. [PubMed: 18827819]

4. Beeghly-Fadiel A, Shu XO, Lu W, Long J, Cai Q, et al. Genetic variation in VEGF family genes and breast cancer risk: a report from the Shanghai Breast Cancer Genetics Study. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2011; 20:33–41.
5. Rodrigues P, Furriol J, Tormo E, Ballester S, Lluch A, et al. The single-nucleotide polymorphisms +936 C/T VEGF and -710 C/T VEGFR1 are associated with breast cancer protection in a Spanish population. *Breast Cancer Research and Treatment*. 2012; 133:769–778. [PubMed: 22315135]
6. Hunter DJ, Kraft P, Jacobs KB, Cox DG, Yeager M, et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. *Nat Genet*. 2007; 39:870–874. [PubMed: 17529973]
7. Barnholtz-Sloan JS, Shetty PB, Guan X, Nyante SJ, Luo J, et al. FGFR2 and other loci identified in genome-wide association studies are associated with breast cancer in African-American and younger women. *Carcinogenesis*. 2010; 31:1417–1423. [PubMed: 20554749]
8. Jara L, Gonzalez-Hormazabal P, Cerceno K, Di Capua GA, Reyes JM, et al. Genetic variants in FGFR2 and MAP3K1 are associated with the risk of familial and early-onset breast cancer in a South-American population. *Breast Cancer Res Treat*. 2013; 137:559–569. [PubMed: 23225170]
9. Chen F, Lv M, Xue Y, Zhou J, Hu F, et al. Genetic variants of fibroblast growth factor receptor 2 (FGFR2) are associated with breast cancer risk in Chinese women of the Han nationality. *Immunogenetics*. 2012; 64:71–76. [PubMed: 21822685]
10. Jia C, Cai Y, Ma Y, Fu D. Quantitative assessment of the effect of FGFR2 gene polymorphism on the risk of breast cancer. *Breast Cancer Res Treat*. 2010; 124:521–528. [PubMed: 20364400]
11. Fejerman L, Stern MC, Ziv E, John EM, Torres-Mejia G, et al. Genetic ancestry modifies the association between genetic risk variants and breast cancer risk among Hispanic and non-Hispanic white women. *Carcinogenesis*. 2013
12. Watnick RS. The role of the tumor microenvironment in regulating angiogenesis. *Cold Spring Harb Perspect Med*. 2012; 2:a006676. [PubMed: 23209177]
13. Soufla G, Sifakis S, Spandidos DA. FGF2 transcript levels are positively correlated with EGF and IGF-1 in the malignant endometrium. *Cancer Lett*. 2008; 259:146–155. [PubMed: 18006148]
14. Olsen DA, Bechmann T, Ostergaard B, Wamberg PA, Jakobsen EH, et al. Increased concentrations of growth factors and activation of the EGFR system in breast cancer. *Clin Chem Lab Med*. 2012; 50:1809–1818. [PubMed: 23089711]
15. Navolanic PM, Steelman LS, McCubrey JA. EGFR family signaling and its association with breast cancer development and resistance to chemotherapy (Review). *Int J Oncol*. 2003; 22:237–252. [PubMed: 12527919]
16. Chrysogelos SA, Dickson RB. EGF receptor expression, regulation, and function in breast cancer. *Breast Cancer Res Treat*. 1994; 29:29–40. [PubMed: 8018962]
17. Wang Y, Tian T, Hu Z, Tang J, Wang S, et al. EGF promoter SNPs, plasma EGF levels and risk of breast cancer in Chinese women. *Breast Cancer Res Treat*. 2008; 111:321–327. [PubMed: 17940864]
18. Henjes F, Bender C, von der Heyde S, Braun L, Mannsperger HA, et al. Strong EGFR signaling in cell line models of ERBB2-amplified breast cancer attenuates response towards ERBB2-targeting drugs. *Oncogenesis*. 2012; 1:e16. [PubMed: 23552733]
19. Idirisinghe PK, Thike AA, Cheok PY, Tse GM, Lui PC, et al. Hormone receptor and c-ERBB2 status in distant metastatic and locally recurrent breast cancer. Pathologic correlations and clinical significance. *Am J Clin Pathol*. 2010; 133:416–429. [PubMed: 20154280]
20. Dahabreh IJ, Murray S. Lack of replication for the association between HER2 I655V polymorphism and breast cancer risk: a systematic review and meta-analysis. *Cancer Epidemiol*. 2011; 35:503–509. [PubMed: 21474413]
21. Goldsmith KT, Gammon RB, Garver RI Jr. Modulation of bFGF in lung fibroblasts by TGF-beta and PDGF. *Am J Physiol*. 1991; 261:L378–385. [PubMed: 1767858]
22. Brogi E, Wu T, Namiki A, Isner JM. Indirect angiogenic cytokines upregulate VEGF and bFGF gene expression in vascular smooth muscle cells, whereas hypoxia upregulates VEGF expression only. *Circulation*. 1994; 90:649–652. [PubMed: 8044933]

23. Slattery ML, John EM, Torres-Mejia G, Lundgreen A, Herrick JS, et al. Genetic variation in genes involved in hormones, inflammation and energetic factors and breast cancer risk in an admixed population. *Carcinogenesis*. 2012; 33:1512–1521. [PubMed: 22562547]
24. Slattery ML, Sweeney C, Edwards S, Herrick J, Baumgartner K, et al. Body size, weight change, fat distribution and breast cancer risk in Hispanic and non-Hispanic white women. *Breast Cancer Res Treat*. 2007; 102:85–101. [PubMed: 17080310]
25. John EM, Horn-Ross PL, Koo J. Lifetime physical activity and breast cancer risk in a multiethnic population: the San Francisco Bay area breast cancer study. *Cancer Epidemiol Biomarkers Prev*. 2003; 12:1143–1152. [PubMed: 14652273]
26. John EM, Phipps AI, Davis A, Koo J. Migration history, acculturation, and breast cancer risk in Hispanic women. *Cancer Epidemiol Biomarkers Prev*. 2005; 14:2905–2913. [PubMed: 16365008]
27. Falush D, Stephens M, Pritchard JK. Inference of population structure using multilocus genotype data: linked loci and correlated allele frequencies. *Genetics*. 2003; 164:1567–1587. [PubMed: 12930761]
28. Pritchard JK, Stephens M, Donnelly P. Inference of population structure using multilocus genotype data. *Genetics*. 2000; 155:945–959. [PubMed: 10835412]
29. Suarez MM, Bautista RM, Almela M, Soriano A, Marco F, et al. *Listeria monocytogenes* bacteremia: analysis of 110 episodes. *Medicina clinica*. 2007; 129:218–221. [PubMed: 17678604]
30. Jacobs EJ, Thun MJ, Connell CJ, Rodriguez C, Henley SJ, et al. Aspirin and other nonsteroidal anti-inflammatory drugs and breast cancer incidence in a large U.S. cohort. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2005; 14:261–264.
31. Yu K, Li Q, Bergen AW, Pfeiffer RM, Rosenberg PS, et al. Pathway analysis by adaptive combination of P-values. *Genetic epidemiology*. 2009; 33:700–709. [PubMed: 19333968]
32. Kai Yu, OL.; William, Wheeler. ARTP Gene and Pathway p-values computed using the Adaptive Rank Truncated Product. 2.0.0. 2011. p. R package
33. Cen YL, Qi ML, Li HG, Su Y, Chen LJ, et al. Associations of polymorphisms in the genes of FGFR2, FGF1, and RBFOX2 with breast cancer risk by estrogen/progesterone receptor status. *Mol Carcinog*. 2012

Table 1

## Description of study population by self-reported ethnicity

	Non-Hispanic White				U. S. Hispanic or Mexican			
	Controls		Cases		Controls		Cases	
	N	%	N	%	N	%	N	%
Total	1586	37.9	1481	41.2	2597	62.1	2111	58.8
Study Site <sup>1</sup>								
4CBCS	1322	83.4	1227	82.8	723	27.8	597	28.3
MCBS	0	0.0	0	0.0	994	38.3	816	38.7
SFBCS	264	16.6	254	17.2	880	33.9	698	33.1
Age (years)								
<40	116	7.3	89	6.0	311	12.0	200	9.5
40-49	408	25.7	409	27.6	831	32.0	713	33.8
50-59	409	25.8	413	27.9	756	29.1	617	29.2
60-69	350	22.1	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	1076	68.5	970	66.5	1499	59.3	1210	59.1
Family history of breast cancer in first-degree relative								
No	1289	84.5	1122	77.5	2326	91.8	1818	87.8
Yes	237	15.5	326	22.5	208	8.2	252	12.2
Estimated Native American Ancestry								
Low (0 - 28%)	1578	99.5	1472	99.4	278	10.7	275	13.0
Intermediate (29 - 70%)	7	0.4	7	0.5	1686	64.9	1393	66.0
High (71 - 100%)	1	0.1	2	0.1	633	24.4	443	21.0
ER/PR Status <sup>2</sup>								
ER+/PR+	NA		695	68.2	NA		605	61.9
ER+/PR-	NA		121	11.9	NA		115	11.8
ER-/PR+	NA		15	1.5	NA		28	2.9

	Non-Hispanic White			U. S. Hispanic or Mexican		
	Controls		Cases	Controls		Cases
	N	%	N	%	N	%
ER-/PR-	NA	188	18.4	NA	229	23.4
Vital Status <sup>2,3</sup>						
Deceased	NA	202	17.1	NA	202	17.5
Alive	NA	982	82.9	NA	950	82.5
Cause of Death <sup>2,3</sup>						
Breast Cancer	NA	102	50.5	NA	115	56.9
Other	NA	100	49.5	NA	87	43.1
SEER Summary Stage <sup>2,3</sup>						
Local	NA	829	71.1	NA	648	59.6
Regional	NA	322	27.6	NA	430	39.6
Distant	NA	15	1.3	NA	9	0.8
Tumor Grade <sup>2,3</sup>						
I - Well Differentiated	NA	267	22.6	NA	191	16.6
II - Moderately Differentiated	NA	463	39.1	NA	434	37.7
III - Poorly Differentiated	NA	336	28.4	NA	394	34.2
IV - Undifferentiated/Anaplastic	NA	18	1.5	NA	24	2.1
Not Determined	NA	100	8.4	NA	109	9.5
Histology <sup>2,3</sup>						
Ductal	NA	866	73.1	NA	891	77.3
Lobular	NA	88	7.4	NA	67	5.8
Mixed Ductal/Lobular	NA	108	9.1	NA	79	6.9
Mucinous	NA	24	2.0	NA	28	2.4
Inflammatory	NA	7	0.6	NA	5	0.4
Tubular	NA	20	1.7	NA	11	1.0
Medullary	NA	14	1.2	NA	16	1.4
Other/Mixed types	NA	57	4.8	NA	55	4.9

<sup>1</sup> 4CBCS= 4 Corners Breast Cancer Study; MBCS = Mexico Breast Cancer Study; SFBCS = San Francisco Bay Area Breast Cancer Study

<sup>2</sup> Information unavailable for the Mexico study site.

3 Among primary invasive breast cancer cases.

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**Table 2**  
**Associations between growth factor related genes and risk of breast cancer: all women combined**

	Controls		Cases		OR <sup>1</sup>	(95% CI)	P <sub>ARTP Gene</sub>	P <sub>ARTP Pathway</sub>
	N	N	N	N				
<i>FGFR2</i> (rs2981582)	CC	1491	1103	1.00			0.0001	0.001
	CT	2009	1749	1.18	(1.06, 1.30)			
	TT	638	708	1.50	(1.31, 1.71)			
<i>PDGFB</i> (rs9622978)	GG	1612	1418	1.00			0.045	
	GT	1903	1653	0.97	(0.88, 1.07)			
	TT	629	489	0.85	(0.74, 0.98)			
<i>PDGFB</i> (rs4821877)	TT	1084	820	1.00				
	TC	2008	1728	1.11	(1.00, 1.25)			
	CC	968	914	1.20	(1.05, 1.36)			
<i>NRG2</i> (rs6895139)	GG/GA	4124	3557	1.00			0.034	
	AA	25	10	0.46	(0.22, 0.96)			
<i>NRG2</i> (rs265155)	GG/GA	4010	3414	1.00				
	AA	138	152	1.29	(1.02, 1.63)			
<i>NRG2</i> (rs1800954)	TT/TC	3834	3227	1.00				
	CC	62	29	0.53	(0.34, 0.84)			
<i>NRG2</i> (rs2436389)	TT	2248	1782	1.00				
	TG/GG	1901	1786	1.12	(1.02, 1.23)			

<sup>1</sup>Odds Ratios (OR) and 95% Confidence Intervals (CI) adjusted for age, study, BMI during the referent year, parity and genetic admixture; table includes only SNPs with statistically significant findings

**Table 3**  
**Associations between growth factor-related genes and breast cancer risk stratified by menopausal status**

	Pre Menopause						Post Menopause					
	Controls			Cases			Controls			Cases		
	N	N	OR <sup>1</sup>	(95% CI)	P <sub>AKTP gene<sup>2</sup></sub>	P <sub>AKTP gene<sup>2</sup></sub>	N	N	OR	(95% CI)	P <sub>AKTP gene<sup>2</sup></sub>	Interaction p-value
<i>EGF</i> (rs4444903)	412	341	1.00		0.12	0.13	689	644	1.00		0.13	0.05
	724	637	1.12	(0.94, 1.35)			1268	1051	0.91	(0.79, 1.04)		
	376	339	1.19	(0.96, 1.47)			595	467	0.88	(0.74, 1.04)		
<i>ERBB2</i> (rs1810132)	630	543	1.00		0.50	0.03	1001	930	1.00		0.03	0.05
	689	609	1.04	(0.89, 1.22)			1185	979	0.90	(0.79, 1.02)		
	194	166	1.05	(0.83, 1.34)			363	255	0.79	(0.65, 0.95)		
<i>FGF1</i> (rs4912868)	589	588	1.00		0.22	0.51	1113	924	1.00		0.51	0.02
	720	566	0.81	(0.69, 0.95)			1118	967	1.07	(0.94, 1.21)		
	204	163	0.83	(0.66, 1.06)			321	272	1.07	(0.89, 1.29)		
<i>FGF1</i> (rs4912876)	749	615	1.00		0.29	0.04	1167	994	1.00		0.04	0.04
	639	558	1.04	(0.89, 1.21)			1119	959	0.98	(0.87, 1.11)		
	125	145	1.33	(1.02, 1.74)			266	211	0.89	(0.73, 1.09)		
<i>NRG2</i> (rs4912894)	534	431	1.00		0.29	0.07	791	702	1.00		0.07	0.04
	695	608	1.03	(0.87, 1.23)			1214	1018	0.90	(0.79, 1.04)		
	248	245	1.11	(0.88, 1.39)			486	400	0.84	(0.71, 1.00)		
<i>NRG2</i> (rs11167875)	507	410	1.00		0.29	0.01	759	688	1.00		0.01	0.01
	728	635	1.06	(0.90, 1.26)			1281	1069	0.87	(0.76, 1.00)		
	278	273	1.16	(0.93, 1.44)			512	407	0.82	(0.69, 0.97)		
<i>NRG2</i> (rs2436389)												

	Pre Menopause						Post Menopause							
	Controls			Cases			Controls			Cases				
	N	OR <sup>1</sup>	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)	N	OR	(95% CI)	P <sub>PARTP gene<sup>2</sup></sub>	Interaction p-value
TT	877	1.00		674	1.00		1318	1.00		1073	1.00			0.04
TG/GG	635	1.25	(1.06, 1.46)	644	1.25	(1.06, 1.46)	1234	1.03	(0.91, 1.16)	1090	1.03	(0.91, 1.16)		

<sup>1</sup> Odds Ratios (OR) and 95% Confidence Intervals (CI) adjusted for age, study, BMI during referent years, parity and genetic admixture; table includes only SNPs with statistically significant findings

<sup>2</sup> Pathway PARTP is 0.028 for pre-menopause and 0.001 for post-menopausal women

**Table 4**  
**Associations between growth factor-related genes and ER and PR tumor status**

	Control		ER+/PR+				ER-/PR-					
	N	OR <sup>I</sup>	(95% CI)	P <sub>ARTIP</sub> <sup>2</sup>	N	OR	(95% CI)	P <sub>ARTIP</sub>	N	OR	(95% CI)	P <sub>ARTIP</sub>
<i>EGF</i> (rs4444903)												
AA	926	393	1.00	0.72	86	1.00		0.01	6	1.00		0.04
AG	1561	637	0.97	(0.84, 1.13)	98	0.66	(0.49, 0.90)		27	2.61	(1.07, 6.38)	
GG	678	268	0.97	(0.80, 1.17)	50	0.78	(0.54, 1.13)		9	1.93	(0.67, 5.54)	
<i>FGF1</i> (rs34001)												
GG	1118	430	1.00	0.66	84	1.00		0.57	14	1.00		0.76
GT	1507	636	1.09	(0.94, 1.26)	108	0.95	(0.70, 1.28)		23	1.24	(0.63, 2.42)	
TT	540	230	1.07	(0.88, 1.29)	43	1.02	(0.69, 1.50)		6	0.91	(0.35, 2.39)	
<i>FGF1</i> (rs152524)												
AA	1284	497	1.00		91	1.00			17	1.00		
AG	1428	603	1.05	(0.91, 1.21)	106	1.01	(0.75, 1.36)		21	1.19	(0.61, 2.29)	
GG	454	198	1.04	(0.85, 1.27)	38	1.11	(0.74, 1.67)		5	0.92	(0.33, 2.59)	
<i>FGF1</i> (rs34021)												
GG	1530	579	1.00	0.12	113	1.00		0.55	19	1.00		0.51
GA	1329	597	1.16	(1.01, 1.33)	97	0.98	(0.74, 1.30)		21	1.30	(0.69, 2.44)	
AA	307	121	1.01	(0.80, 1.28)	25	1.10	(0.70, 1.73)		3	0.84	(0.24, 2.87)	
<i>FGF2</i> (rs11938826)												
CC	1988	833	1.00		148	1.00			28	1.00		
CG	1006	423	1.04	(0.90, 1.20)	74	1.02	(0.76, 1.37)		12	0.79	(0.40, 1.57)	
GG	169	41	0.63	(0.44, 0.89)	13	1.16	(0.64, 2.10)		3	1.06	(0.31, 3.56)	
<i>FGF2</i> (rs1960669)												
GG	2329	877	1.00		159	1.00			30	1.00		
GT/TT	575	271	1.21	(1.03, 1.43)	41	1.01	(0.70, 1.45)		7	1.01	(0.43, 2.35)	
<i>FGFR2</i> (rs2981582)												
CC	1123	386	1.00	0.0001	65	1.00		0.02	11	1.00		0.09
CT	1552	632	1.19	(1.02, 1.38)	127	1.41	(1.04, 1.92)		22	1.42	(0.68, 2.94)	
TT	483	274	1.66	(1.37, 2.00)	43	1.54	(1.03, 2.31)		10	2.10	(0.89, 5.00)	

Control	ER+/PR+					ER+/PR-					ER-/PR-					
	N	OR <sup>1</sup>	(95% CI)	P <sub>PARTP</sub> <sup>2</sup>	N	OR	(95% CI)	P <sub>PARTP</sub>	N	OR	(95% CI)	P <sub>PARTP</sub>	N	OR	(95% CI)	P <sub>PARTP</sub>
<i>PDGFB</i> (rs9622978)																
GG/GT	1093	1.00		0.08	202	1.00		0.49	38	1.00		0.90	367	1.00		0.08
TT	528	0.89	(0.74, 1.06)		32	0.78	(0.53, 1.15)		5	0.69	(0.27, 1.76)		47	0.65	(0.47, 0.90)	
<i>PDGFB</i> (rs750781)																
CC	1839	1.00			123	1.00			27	1.00			249	1.00		
CA/AA	1325	0.87	(0.76, 0.99)		111	1.24	(0.94, 1.63)		16	0.90	(0.47, 1.70)		166	0.95	(0.77, 1.18)	
<i>PDGFB</i> (rs2857402)																
CC	1865	1.00			127	1.00			28	1.00			256	1.00		
CG/GG	1295	0.87	(0.76, 1.00)		106	1.18	(0.90, 1.56)		15	0.84	(0.44, 1.61)		158	0.91	(0.74, 1.14)	
<i>NRG2</i> (rs2431384)				0.13				0.98				0.39				0.39
AA	2309	1.00			175	1.00			34	1.00			302	1.00		
AG	789	0.91	(0.78, 1.06)		52	0.86	(0.62, 1.19)		9	0.75	(0.36, 1.58)		110	1.06	(0.84, 1.33)	
GG	62	0.98	(0.61, 1.56)		6	1.25	(0.53, 2.95)		0				2	0.23	(0.06, 0.95)	
<i>NRG2</i> (rs1800954)																
TT/TC	2860	1.00			196	1.00			36	1.00			341	1.00		
CC	52	0.51	(0.26, 0.97)		4	1.08	(0.38, 3.03)		1	1.62	(0.22, 12.17)		4	0.64	(0.23, 1.79)	
<i>NRG2</i> (rs2436389)																
TT	1536	1.00			106	1.00			18	1.00			182	1.00		
TG/GG	1629	0.85	(0.89, 1.16)		129	1.13	(0.86, 1.49)		25	1.47	(0.78, 2.76)		233	1.26	(1.02, 1.56)	

<sup>1</sup> Odds Ratios (OR) and 95% Confidence Intervals (CI) are adjusted for age, study, BMI during referent year, parity and genetic admixture form U.S. Studies. Table includes only SNPs with statistically significant findings

<sup>2</sup> P<sub>PARTP</sub> values in table are for gene; the overall pathway p value for ER+/PR+ tumors was 0.001; for ER+/PR- tumors was 0.06; for ER-/PR+ was 0.29, and for ER-/PR- was 0.33.

Table 5

## Interaction between genes related to growth factors

Gene 1	Gene 2	wt 1/variant 2 OR (95% CI) <sup>1</sup>	variant 1/wt 2 OR (95% CI)	variant 1/variant 2 OR (95% CI)	p interaction
<i>EGFR</i>					
(rs6944906)	<i>FGF1</i> (rs152528)	0.76 (0.59,0.99)	0.82 (0.71,0.95)	0.785 (0.70,1.05)	0.02
	<i>FGF2</i> (rs1960669)	0.83 (0.67,1.03)	0.86 (0.77,0.96)	1.05 (0.89,1.24)	<0.01
(rs1558544)	<i>FGF2</i> (rs308395)	0.85 (0.65,1.10)	0.67 (0.50,0.89)	0.83 (0.30,2.31)	<0.01
	<i>FGF2</i> (rs167428)	0.79 (0.63,0.98)	0.66 (0.47,0.91)	1.21 (0.62,2.38)	0.01
	<i>FGF2</i> (rs11837725)	0.84 (0.66,1.08)	0.62 (0.46, 0.83)	0.70 (0.19,2.49)	0.02
	<i>FGF2</i> (rs308441)	0.72 (0.56,0.93)	0.70 (0.52,0.94)	1.50 (0.61,3.71)	<0.01
(rs6593205)	<i>FGF2</i> (rs1476214)	1.05 (0.83,1.33)	0.67 (0.54,0.83)	1.27 (0.88,1.83)	0.03
	<i>FGF2</i> (rs3789138)	0.93 (0.75,1.14)	0.68 (0.53,0.87)	1.11 (0.82,1.51)	0.03
	<i>FGF2</i> (rs3804158)	0.96 (0.78,1.18)	0.66 (0.51,0.86)	1.16 (0.87,1.57)	0.02
(rs17151957)	<i>EGF</i> (rs4444903)	0.90 (0.75,1.08)	0.61 (0.43,0.86)	0.97 (0.69,1.36)	0.03
(rs6970262)	<i>FGF1</i> (rs4912876)	0.86 (0.68,1.09)	0.87 (0.69,1.10)	1.60 (1.00,2.54)	0.01
(rs723527)	<i>FGF2</i> (rs308441)	0.69 (0.48,0.99)	0.90 (0.76,1.07)	1.12 (0.72,1.75)	0.02
(rs3752651)	<i>FGF1</i> (rs34019)	0.86 (0.76,0.97)	0.96 (0.72,1.29)	2.60 (1.30,5.17)	<0.01
<i>ERBB2</i>					
(rs1810132)	<i>FGF1</i> (rs34016)	0.79 (0.55,1.13)	0.77 (0.64,0.93)	1.70 (0.87,3.34)	0.01
(rs1136201)	<i>EGFR</i> (rs11770531)	0.71 (0.44,1.15)	1.04 (0.94,1.15)	0.25 (0.10,0.62)	0.04
<i>FGFR2</i>					
(rs2981582)	<i>FGF2</i> (rs7700205)	1.33 (1.14,1.55)	0.80 (0.66,0.97)	1.85 (1.44,2.38)	<0.01
	<i>FGF2</i> (rs17408757)	1.40 (1.21,1.62)	0.87 (0.71,1.07)	1.79 (1.36,2.34)	0.03
	<i>FGF2</i> (rs1960669)	1.36 (1.17,1.58)	0.87 (0.70,1.09)	1.97 (1.47,2.63)	0.01
	<i>FGF2</i> (rs6534365)	1.24 (1.03,1.50)	1.03 (0.77,1.38)	1.65 (1.12,2.43)	0.03
	<i>EGFR</i> (rs17586365)	0.84 (0.44,1.61)	1.40 (1.21,1.63)	7.77 (2.24,26.93)	0.03
	(rs6954351)	1.27 (0.61,2.62)	1.63 (1.40,1.89)	2.22 (0.85,5.78)	0.02
<i>PDGFB</i>					
(rs9622978)	<i>FGF1</i> (250092)	0.95 (0.82,1.09)	1.03 (0.91,1.17)	0.59 (0.44,0.79)	<0.01
	<i>FGF1</i> (rs4912868)	0.70 (0.57,0.86)	0.91 (0.78,1.07)	1.16 (0.82,1.62)	<0.01
(rs2247128)	<i>FGF1</i> (rs4912868)	0.87 (0.66,1.13)	0.88 (0.73,1.07)	1.97 (1.07,3.63)	0.04



Gene 1	Gene 2	wt 1/variant 2 OR (95% CI) <sup>1</sup>	variant 1/wt 2 OR (95% CI)	variant 1/variant 2 OR (95% CI)	p interaction
(rs6001512)	FGF2 (rs308435)	1.01 (0.85,1.20)	1.02 (0.91,1.14)	1.47 (1.13,1.93)	0.03
<i>NRG2</i>					
(rs265159)	EGFR (rs2280653)	0.65 (0.45,0.92)	1.03 (0.82,1.30)	1.85 (0.71,4.81)	<0.01
(rs3863190)	FGF1 (rs1609763)	1.02 (0.83,1.25)	1.08 (0.89,1.33)	1.72 (1.01,2.95)	0.04
	EGFR (rs9642391)	0.93 (0.78,1.11)	0.83 (0.51,1.35)	8.47 (1.91,37.54)	0.02
	(rs2330951)	1.00 (0.81,1.25)	1.59 (1.03,2.46)	0.68 (0.22,2.10)	0.02
	(rs2280653)	0.95 (0.71,1.27)	1.73 (1.14,2.62)	0.44 (0.05,4.29)	0.05
	FGF1 (rs34019)	0.95 (0.84,1.09)	1.52 (1.05,2.21)	0.49 (0.21,1.14)	<0.01
(rs265155)	EGFR (rs12671550)	1.00 (0.87,1.16)	1.73 (1.20,2.50)	0.74 (0.36,1.51)	0.02
(rs2916092)	EGFR (rs11770531)	0.23 (0.12,0.46)	0.97 (0.82,1.14)	0.98 (0.24,3.94)	<0.01
(rs4912894)	PDGFB (rs4821877)	1.32 (1.05,1.66)	1.07 (0.81,1.41)	0.92 (0.71,1.21)	0.05
(rs1800954)	EGFR (rs172718945)	1.07 (0.97,1.18)	1.03 (0.48,2.23)	0.42 (0.24,0.73)	0.04
	(rs17151957)	0.96 (0.80,1.15)	0.34 (0.18,0.66)	1.33 (0.18,9.57)	0.04
rs(1422187)	EGFR (rs4947979)	1.60 (1.13,2.26)	1.17 (0.89,1.54)	0.67 (0.26,1.73)	0.01
(rs197197)	FGF2 (rs11938826)	0.65 (0.44,0.96)	0.86 (0.72,1.01)	0.77 (0.52,1.16)	0.01
(rs11746363)	EGFR (rs917880)	0.83 (0.70,0.98)	0.68 (0.45,1.02)	0.91 (0.53,1.57)	0.05
(rs13173983)	EGFR (rs2280653)	0.79 (0.56,1.11)	0.72 (0.56,0.93)	0.50 (0.13,1.93)	0.02
(rs6580353)	FGF1 (rs152528)	1.08 (0.88,1.31)	0.97 (0.69,1.35)	0.55 (0.33,0.92)	0.05
	EGFR (rs11770531)	0.81 (0.46,1.42)	1.03 (0.86,1.22)	0.10 (0.01,0.76)	0.02
	FGF2 (rs11938826)	0.72 (0.53,0.97)	0.90 (0.72,1.12)	1.61 (0.88,2.96)	0.03
(rs2436389)	EGFR (rs11487218)	1.14 (0.88,1.48)	1.25 (1.10,1.42)	0.97 (0.77,1.23)	0.01
	(rs10225877)	1.42 (0.96,2.11)	1.26 (1.13,1.41)	0.96 (0.6,1.41)	<0.01
	(rs6944906)	0.85 (0.72,0.97)	0.98 (0.84,1.15)	1.02 (0.89,1.17)	0.04

<sup>1</sup> Odds Ratios (OR) and 95% Confidence Intervals (CI) adjusted for age, study, BMI during the referent year, parity and genetic admixture; table includes only statistically significant interactions

Table 6

## Associations between variants in growth factor-related genes and survival

	All Women				0 - 28% NA Ancestry				29 - 100% NA Ancestry				Interaction p-value	
	Deaths/Person Year	HR <sup>1</sup>	(95% CI)	P <sub>ARTP</sub> <sup>2</sup>	Deaths/Person Year	HR	(95% CI)	P <sub>ARTP</sub>	Deaths/Person Year	HR	(95% CI)	P <sub>ARTP</sub>	raw	
<b>All-Cause Mortality</b>														
<i>ERBB2</i> (rs1810132)				0.25				0.003				0.12	0.0007	
TT	175/8834	1.00			102/5833	1.00			73/3001	1.00				
TC	178/9266	0.99	(0.80, 1.22)		108/5114	1.25	(0.95, 1.64)		70/4152	0.70	(0.50, 0.97)			
CC	51/2373	1.13	(0.83, 1.55)		33/1159	1.74	(1.17, 2.58)		18/1214	0.67	(0.40, 1.12)			
<i>ERBB2</i> (rs4252596)													0.03	
CC	348/16896	1.00			204/9248	1.00			144/7647	1.00				
CA/AA	56/3568	0.78	(0.59, 1.04)		39/2848	0.64	(0.45, 0.90)		17/720	1.24	(0.75, 2.06)			
<i>FGF1</i> (rs17099156)				0.04				0.007				0.18		
GG	257/12989	1.00			151/7881	1.00			106/5108	1.00			0.01	
GA	121/6676	0.92	(0.74, 1.14)		73/3856	1.04	(0.78, 1.37)		48/2820	0.79	(0.56, 1.12)			
AA	26/796	1.68	(1.12, 2.52)		19/369	2.75	(1.70, 4.46)		7/426	0.75	(0.35, 1.63)			
<i>FGF1</i> (rs6893408)													0.17	
GG	293/14658	1.00			174/8766	1.00			119/5892	1.00				
GA	97/5350	0.95	(0.75, 1.19)		57/3107	0.94	(0.70, 1.27)		40/2243	0.95	(0.66, 1.36)			
AA	14/466	1.56	(0.91, 2.66)		12/233	2.67	(1.48, 4.82)		2/232	0.45	(0.11, 1.81)			
<i>FGF1</i> (rs6580256)													0.02	
CC	288/14391	1.00			195/9172	1.00			93/5219	1.00				
CT/TT	116/6082	0.91	(0.73, 1.14)		48/2934	0.71	(0.52, 0.98)		68/3148	1.21	(0.88, 1.65)			
<i>FGF1</i> (rs152524)													0.17	
AA	146/8104	1.00			72/3801	1.00			74/4303	1.00				
AG	192/9391	1.22	(0.98, 1.51)		126/6022	1.14	(0.85, 1.52)		66/3369	1.28	(0.91, 1.79)			
GG	66/2977	1.31	(0.98, 1.77)		45/2283	1.11	(0.77, 1.62)		21/695	1.81	(1.10, 2.97)			
<i>FGF1</i> (rs6884797)													0.45	
CC	287/15814	1.00			171/9265	1.00			116/6549	1.00				
CA/AA	116/4654	1.40	(1.13, 1.74)		71/2836	1.33	(1.01, 1.75)		45/1818	1.57	(1.11, 2.23)			
<i>NRG2</i> (rs6895139)				0.30				0.59				0.76	0.56	
GG	358/17636	1.00			214/10478	1.00			144/7158	1.00				
GA/AA	45/2824	0.73	(0.54, 1.00)		29/1628	0.77	(0.52, 1.15)		16/1196	0.66	(0.39, 1.10)			
<i>NRG2</i> (rs11745110)													0.21	
GG	269/14486	1.00			181/9124	1.00			88/5362	1.00				

	All Women				0 - 28% NA Ancestry				29 - 100% NA Ancestry				Interaction p-value	
	Deaths/Person Year	HR <sup>1</sup>	(95% CI)	P <sub>ARTP</sub> <sup>2</sup>	Deaths/Person Year	HR	(95% CI)	P <sub>ARTP</sub>	Deaths/Person Year	HR	(95% CI)	P <sub>ARTP</sub>	raw	
GA/AA	77/3263	1.28	(1.00, 1.66)		51/2190	1.15	(0.84, 1.57)		26/1074	1.64	(1.05, 2.55)			
NRG2 (rs1422187)														
TT	257/12768	1.00			152/7434	1.00			105/5334	1.00			0.91	
TC	133/6633	1.01	(0.82, 1.25)		82/3904	1.04	(0.79, 1.36)		51/2729	0.94	(0.67, 1.32)			
CC	13/1068	0.54	(0.31, 0.95)		9/768	0.51	(0.26, 1.00)		4/300	0.60	(0.22, 1.65)			
<b>Breast Cancer Mortality</b>														
ERBB2 (rs1810132)				0.53				0.053				0.06	0.003	
TT	101/8834	1.00	(0.68, 1.21)		54/5833	1.00			47/3001	1.00				
TC	91/9266	0.91	(0.66, 1.60)		56/5114	1.26	(0.87, 1.84)		35/4152	0.58	(0.37, 0.90)			
CC	25/2373	1.03			15/1159	1.73	(0.97, 3.09)		10/1214	0.58	(0.29, 1.15)			
ERBB2 (rs4252596)														
CC	186/16896	1.00	(0.55, 1.19)		104/9248	1.00			82/7647	1.00			0.08	
CA/AA	31/3568	0.81			21/2848	0.65	(0.40, 1.04)		10/720	1.35	(0.69, 2.61)			
FGF1 (rs152524)				0.15				0.14				0.42		
AA	80/8104	1.00			39/3801	1.00			41/4303	1.00			0.03	
AG	100/9391	1.21	(0.90, 1.64)		64/6022	1.05	(0.70, 1.57)		36/3369	1.32	(0.84, 2.08)			
GG	37/2977	1.35	(0.90, 2.02)		22/2283	0.93	(0.55, 1.56)		15/695	2.36	(1.27, 4.37)			
FGF1 (rs6884797)														
CC	148/15814	1.00			82/9265	1.00			66/6549	1.00			0.54	
CA/AA	69/4654	1.58	(1.18, 2.10)		43/2836	1.72	(1.19, 2.49)		26/1818	1.46	(0.92, 2.30)			
FGF1 (rs6893408)														
GG	159/14658	1.00			92/8766	1.00			67/5892	1.00			0.82	
GA	49/5350	0.89	(0.65, 1.23)		26/3107	0.80	(0.52, 1.24)		23/2243	1.02	(0.63, 1.65)			
AA	9/466	2.01	(1.03, 3.95)		7/233	2.69	(1.24, 5.84)		2/232	1.01	(0.25, 4.16)			
NRG2 (rs11738832)				0.34				0.48				0.98		
AA	73/5637	1.00			36/2729	1.00			37/2908	1.00			0.27	
AG	103/10007	0.82	(0.60, 1.10)		64/5890	0.92	(0.61, 1.39)		39/4117	0.71	(0.45, 1.12)			
GG	40/4799	0.66	(0.44, 0.97)		24/3457	0.53	(0.32, 0.90)		16/1342	0.98	(0.54, 1.77)			
NRG2 (rs1422187)														
TT	136/12768	1.00			75/7434	1.00			61/5334	1.00			0.73	
TC	76/6633	1.09	(0.82, 1.45)		48/3904	1.20	(0.83, 1.73)		28/2729	0.92	(0.59, 1.44)			
CC	5/1068	0.41	(0.17, 1.00)		2/768	0.22	(0.05, 0.88)		3/300	0.92	(0.28, 2.97)			

<sup>1</sup> Hazard Ratios (HR) and 95% Confidence Intervals (CI) adjusted for age, study, SEER summary Stage, and genetic admixture; data limited to U.S. studies; table includes only statistically significant findings.

<sup>2</sup> Pathway PARTPs for all-cause mortality were 0.25 for all participants, 0.005 for 0-25% NA ancestry and 0.61 for 29-100% NA ancestry; for breast cancer mortality these values were 0.62, 0.39, and 0.46 respectively

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