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Vitamin D-Related Gene Polymorphisms, Plasma 25-Hydroxyvitamin D, and Breast Cancer Risk

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Abstract

Purpose—Studies of vitamin D pathway genetic variants in relation to cancer risk have been inconsistent. We examined associations between vitamin D-related genetic polymorphisms, plasma 25-hydroxyvitamin D [25(OH)D], and breast cancer risk.

Methods—In a population-based case-control study of 967 incident breast cancer cases and 993 controls, we genotyped 25 polymorphisms encoding the vitamin D receptor (*VDR*) gene, 1 α -hydroxylase (*CYP27B1*), 24-hydroxylase (*CYP24A1*), and vitamin D binding protein (*GC*) and measured plasma 25(OH)D. We used multivariable logistic regression to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CI).

Results—Among *CYP24A1* polymorphisms, rs6068816 was associated with a 72% reduction in breast cancer risk (TT vs. CC, OR: 0.28, 95%CI: 0.10–0.76; $p_{\text{trend}}=0.01$), but for rs13038432, the 46% decrease included the null value (GG vs. AA, OR: 0.54, 95%CI: 0.17–1.67; $p_{\text{trend}}=0.03$). Increased risk that included the null value was noted for *CYP24A1* rs3787557 (CC vs. TT, OR: 1.34, 95% CI: 0.92–1.89). The *VDR* polymorphism, TaqI (rs731236), was associated with a 26% risk reduction (TT vs. CC, OR: 0.74, 95%CI: 0.56–0.98; $p_{\text{trend}}=0.01$). For other polymorphisms, ORs were weak and included the null value. The inverse association for plasma 25(OH)D with

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breast cancer was more pronounced (OR: 0.43, 95%CI: 0.27–0.68) among women with the common allele for *CYP24A*, rs927650 (p for interaction on a multiplicative scale=0.01).

Conclusion—Breast cancer risk may be associated with specific vitamin D-related polymorphisms, particularly *CYP24A1*. Genetic variation in the vitamin D pathway should be considered when designing potential intervention strategies with vitamin D supplementation.

Keywords

breast cancer; vitamin D related gene polymorphisms; plasma 25-hydroxyvitamin D; *CYP24A1*

Introduction

Vitamin D in the body comes from two main sources, endogenous production from sun exposure (accounting for up to 90%) or ingestion of food or supplements [1]. Epidemiologic studies have consistently reported reduced breast cancer incidence and mortality associated with greater exposure to sunlight and ultraviolet B (UVB) irradiation [2–11]. However, results for studies evaluating dietary and supplemental intake of vitamin D and breast cancer risk are mixed [12–18]. Circulating 25-hydroxyvitamin D [25(OH)D] is an objective measure of vitamin D status from sunlight exposure, dietary, or supplement intake. Two recent meta-analysis of prospective studies showed overall 25(OH)D blood levels are associated with reduced breast cancer risk [19,20]. However, three recent prospective studies observed no association between 25(OH)D levels and breast cancer risk [21–23] and only one recent prospective study found an inverse association among whites, but not other ethnic groups [24].

Several enzymatic steps are involved in vitamin D metabolism. Genetic variants involved in vitamin D metabolism potentially modify cancer risk [25]. UVB exposure converts 7-dehydrocholesterol into vitamin D₃ (cholecalciferol). Metabolism is initiated when vitamin D₃ is hydroxylated in the liver to 25(OH)D through a reaction catalyzed by 25-hydroxylase enzyme. If calcium levels drop, parathyroid hormone (PTH) is released and activates 1 α -hydroxylase (encoded by *CYP27B1*) that hydroxylates 25(OH)D to the active metabolite, 1,25-dihydroxyvitamin D [1,25(OH)₂D]. 1,25(OH)₂D binds to the vitamin D receptor (*VDR*), a ligand-dependent transcription factor, that regulates transcription of a number of genes involved in cell proliferation, differentiation, apoptosis, growth factor signaling, and immunomodulation [25,26]. Both 25(OH)D and 1,25(OH)₂D can also be degraded into less active forms by 24-hydroxylase (encoded by *CYP24A1*). The group-specific component (*GC*) gene encodes the vitamin D-binding protein (DBP), which facilitates the transport of vitamin D metabolites.

Vitamin D pathway genetic polymorphisms may influence breast cancer risk. Most well-studied are vitamin D receptor (*VDR*) polymorphisms. A comprehensive review found no evidence of a consistent association between *VDR* polymorphisms and breast cancer risk [27]. Studies of single nucleotide polymorphisms (SNPs) in *GC* found no significant association with breast cancer risk [25,28,29]. *CYP27B1* and *CYP24A1* are involved in the activation and degradation of 25(OH)D and 1,25(OH)₂D. Only five studies examined the association between SNPs on these genes and breast cancer risk [25,28–31]. A review

suggests that some SNPs on these genes may be associated with breast cancer risk, but results are inconclusive [32].

Variations in these genes may influence vitamin D synthesis and levels of circulating vitamin D. Potential interactions between genotypes and vitamin D levels have not been adequately addressed in epidemiologic studies. Only three previous studies examined interactions between circulating 25(OH)D and *VDR* gene polymorphisms, specifically those detected by digestion with *BsmI* (rs1544410) and *FokI* (rs10735810) [33–35]. Effect modification of *GC* polymorphisms, *CYP27B1* and *CYP24A1*, may also be important to breast cancer development. Less is known about these vitamin D-related genes and their association with breast cancer risk and interaction with circulating 25(OH)D.

Among participants in a population-based case-control study, the Long Island Breast Cancer Study Project (LIBCSP), we previously observed an inverse association between circulating 25(OH)D and breast cancer risk [36]. Our objective here was to examine whether polymorphisms in genes involved in the vitamin D pathway may modify the association between 25(OH)D and breast cancer in an effort to identify susceptible subgroups of the population who may be at highest risk or who may benefit most from vitamin D exposure.

Materials and Methods

This study utilizes the LIBCSP, a population-based case-control study conducted on Long Island, New York [37]. Full details have been reported previously [37]. Institutional Review Board approval was obtained from all participating institutions.

Study Population

Breast cancer cases were women 20 years of age or older, residents of Nassau or Suffolk County, English-speaking, and newly diagnosed with *in situ* or invasive breast cancer between August 1, 1996 and July 31, 1997. Eligible cases were identified through daily or weekly contact with the 28 hospitals in these two counties, and three hospitals in New York City that treat Long Island residents diagnosed with breast cancer. Controls were women without breast cancer identified by random digit dialing for women under 65 years of age and through Health Care Finance Administration (now the Center for Medicare and Medicaid Services) rosters for women 65 years or older. Controls were frequency matched to the expected age distribution of the cases by 5-year age groups.

Trained interviewers administered the structured two-hour case-control questionnaire where respondents were asked about breast cancer risk factors and demographic characteristics [37]. In-person interviews were completed by 82.1% (n=1,508) of the eligible cases and 62.7% (1,556) of the eligible controls. Respondents ranged in age from 20 to 98 years, were primarily postmenopausal (67%), and 93% self-reported as white, 5% black, and 2% other, which is consistent with the underlying racial distribution of the study area at the time of data collection [37].

Medical records of cases were abstracted to obtain information on tumor characteristics of the first primary breast cancer. Non-fasting blood samples were obtained at the time of the

interview from 73.1% of the case and 73.3% of the control respondents (n=1102 and 1141, respectively). Samples were collected prior to chemotherapy for 77.2% (851/1102) of the case respondents [37]. Plasma 25(OH)D measurements are absent in 6.9% of cases and 5.8% of controls, due to insufficient sample to complete the assay [36].

We limited the study reported here to white women due to population stratification concerns, and thus our final sample size was 967 breast cancer cases and 993 controls. LIBCSP case and control participants who reported their race as white and with both DNA and serum available for this study had a mean age of 58.6 and 56.5 years, respectively [36]. Cases more often reported nulliparity, a first-degree family history of breast cancer and history of benign breast disease. Season of blood draw was also slightly different between cases and controls. Cases had higher percentage of women with blood drawn in October to December as compared to controls (31.5% vs. 27.8%, respectively). However, controls had higher percentage of blood drawn in January to March as compared to cases (24.5% vs. 18.2%, respectively). For the remaining months, April to September the frequency of blood draws was similar between cases and controls.

Measurement of Plasma 25(OH)D

Quantification of 25(OH)D in plasma was done via Diasorin radioimmunoassay (RIA) method. Prior to measurement, plasma samples were stored at -80°C . Samples were analyzed in batches between September and December 2007 using eight lots of the assay, as described previously [36]. Quality controls were utilized to assess inter-assay accuracy and precision. During each run quality control (QC) samples (n=5) were run together with the study samples. QC samples (n=2; 17.3 and 50.4 ng/mL) provided by Diasorin, pooled plasma sample (n=1; 23.6 ng/mL) and commercially available external QC samples (n=2; 63.9 and 107.9 ng/mL). The inter-assay precision, determined for each QC from n=56 runs was 14.2, 15.7, 16.4, 14.2 and 5.7%, respectively. In addition, the lab successfully ran external proficiency samples from the UK-based vitamin D proficiency program DEQAS. Measurement of plasma 25(OH)D were performed in the laboratory of Dr. Serge Cremers at Columbia University Medical Center (CUMC).

Genotyping Assays

We selected 35 SNPs for genotyping with known or suspected impact on the vitamin D pathway or that had been associated with breast cancer in previous studies [27,32]. They included 20 SNPs in *VDR*: rs6823, *BsmI* (rs1544410), rs2071358, rs2107301, rs2239181, rs2239182, rs2408876, rs2544038, rs3782905, rs4073729, rs4760674, rs7299460, *TaqI* (rs731236), rs739837, rs7974708, *Apal* (rs7975232), *FokI* (rs10735810), rs10875694, rs11168287, and rs11168314; 12 SNPs from 24-hydroxylase (*CYP24A1*): rs927650, rs2181874, rs2296241, rs2244719, rs2245153, rs2585428, rs2762939, rs3787557, rs4809960, rs6022999, rs6068816, and rs13038432; two from the vitamin D-binding protein (*GC*): rs4588 and rs7041; and one from 1 α -hydroxylase (*CYP27B1*): rs4646537.

As previously described, genomic DNA was extracted from mononuclear cells in whole blood separated by Ficoll (Sigma Chemical Co., St. Louis, MO) and washed twice with phosphate-buffered saline [37]. Pelleted cells were frozen at -80°C until DNA isolation by

standard phenol and chloroform/isoamyl alcohol extraction. Master DNA 96-well plates containing 10 ng/μl were used to make replica plates. Genotyping of the SNPs was performed by the fluorogenic 5'-nuclease or TaqMan assay, using the TaqMan Core Reagent Kit (Applied Biosystems, Foster City, California). Polymerase chain reactions were carried out by using standard conditions recommended by the manufacturer. The fluorescence profile of each well was measured in an ABI 7500HT Sequence Detection System and the results analyzed with Sequence Detection Software (Applied Biosystems). Controls for genotype at each locus and two no DNA controls were included on each plate. Any samples that were outside the parameters defined by the controls were identified as non-informative and were retested. Four SNPs VDR (rs2239182, rs2239181), CYP24A1 (rs6068816) had concordance >98%. Most other SNPs fell between 95–98%, except four SNPs with concordance below 95% (rs2107301 and rs6823 had 94%, rs4760674 91% and rs4073729 85% concordance) [38]. All SNPs had a call rate of 95% or better, except four: VDR (rs1544410: 89.1%; rs3782905 93.0%), CYP24A1 (rs2762939: 93.3%), and GC (rs7041: 94.6%). Laboratory personnel were blinded to case/control status. Genotyping assays were performed in the laboratory of Dr. Regina Santella at CUMC.

Statistical Methods

For each of the 35 polymorphisms assayed, white subjects were divided into three groups based on genotype. We tested for deviation from Hardy-Weinberg equilibrium (HWE) among controls for each polymorphism using observed genotype frequencies and a χ^2 test with one degree of freedom [39]. VDR (*FokI*, rs10735810) had significant departure from HWE and CYP27B1 (rs464537) had a minor allele frequency (MAF) of <5%; thus, both SNPs were excluded. We also excluded the four SNPs with concordance below 95%. The following ten SNPs were in linkage disequilibrium: VDR *Apal* (rs7975232) and VDR rs739837; VDR *BsmI* (rs1544410) and VDR *TaqI* (rs731236); VDR rs3782905 and VDR rs7974708; CYP24A1 rs2585428 and CYP24A1 rs2296241; CYP24A1 rs4809960 and CYP24A1 rs2245153. Given the relative importance of *BsmI* and *TaqI* in other published literature, we elected to include these SNPs. We used *Apal* instead of rs739837 as previous studies have suggested an association between *Apal* and breast cancer, whereas rs739837 has only been associated with fair skin and melanoma risk [40,41]. We selected rs3782905 and rs4809960 instead of rs7974708 and rs2245153, respectively; due to previous studies suggesting an association with prostate cancer prognosis [42], whereas to our knowledge rs7974708 has not been investigated in relation to cancer. For the CYP24A1 SNPs, we selected rs2585428, instead of rs2296241, because a prior study found no association between breast cancer risk and rs2296241 [43]. Thus, the final number of SNPs included in our statistical analyses was 25.

Quantile regression was used to compare plasma 25(OH)D concentrations across all three genotypes and comparing a dominant model among controls [44]. We used log transformed plasma 25(OH)D concentrations, to normalize the distribution of 25(OH)D. To obtain plasma 25(OH)D concentrations that are adjusted for seasonal trend, we estimated the trend using a sine function among the controls, then we subtracted the estimated trend from measured plasma 25(OH)D. We used these adjusted values for all analyses that incorporated 25(OH)D.

We examined the association between genotype and breast cancer risk by unconditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) [45]. The genotype that was homozygous for the common allele was used as the referent category.

We conducted polytomous logistic regression for the association between genotype and subgroups of breast cancer defined by tumor characteristics [45]. ORs were estimated with cases classified by stage of disease (*in situ* vs. invasive) and hormone receptor status (estrogen receptor (ER)+ or progesterone receptor (PR)+ vs. ER-/PR- or ER+/PR+ vs. ER-/PR-). The ratio of the ORs (ROR) was used as an indicator of etiological heterogeneity across disease stage and hormone receptor subtype [46].

Effect modification of plasma 25(OH)D across level of genotype was evaluated on a multiplicative scale comparing the likelihood ratio tests of logistic regression models with and without interaction terms [45]. Plasma 25(OH)D was divided into two categories (<19.1 and ≥19.1 ng/mL), based on the lowest quartile of 25(OH)D vs. all above. Multiplicative interactions were assessed using indicator variables, where low plasma 25(OH)D (<19.1 ng/mL) was the referent category in a dominant genetic model, stratified by homozygous common allele and heterozygous or homozygous minor allele.

We identified potential confounders using a directed acyclic graph (DAG): first degree family history of breast cancer, body mass index (BMI), oral contraceptive use, alcohol consumption, smoking, hormone replacement use, breastfeeding, and mammogram use. Potential confounders were included in the final models as a confounder if their inclusion significantly changed the log-likelihood of the model. Only two of these variables (family history of breast cancer and mammogram use) confounded the models. Therefore, all final statistical models include adjustment for age, first-degree family history of breast cancer, and mammogram use.

To aid in the interpretation of our results, we accounted for multiple comparisons using the Bonferroni correction [47]. Given we examined 25 SNPs, the corrected p-value denoting a significant association was $p < 0.002$. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Among white control women with DNA and serum samples available for this study, we found a difference in median plasma 25(OH)D concentrations across genotypes for several polymorphisms, as shown in Table 1. For almost half of control participants (44.9%), regardless of genotype, the geometric mean of plasma 25(OH)D was <30 ng/mL. For two *VDR* SNPs (rs2071358, rs2408876), we observed different geometric mean 25(OH)D levels across genotype. For the *CYP27A1* (rs13038432), it appears that geometric mean plasma 25(OH)D levels are lower among those with the GG genotype than those with AA genotype. For both *GC* polymorphisms (rs4588, rs7041), the lowest median plasma 25(OH)D was among those with homozygous minor alleles ($p=0.001$ and $p=0.001$, respectively).

As shown in Table 2, *CYP24A1* rs6068816 was associated with a 72% reduction in breast cancer risk (TT vs. CC, OR: 0.28, 95% CI: 0.10–0.76, $p_{\text{trend}}=0.01$). Increased breast cancer

risk was noted for *CYP24A1* rs6022999, rs2181874 and rs3787557, however the confidence intervals included the null value (GG vs. AA, OR: 1.35 95% CI: 0.95–1.90, $p_{\text{trend}}=0.11$; AA vs. GG, OR: 1.37, 95% CI: 0.96–1.95, $p_{\text{trend}}=0.11$; CC vs. TT, OR: 1.34, 95% CI: 0.92–1.89, $p_{\text{trend}}=0.49$, respectively). For *VDR* polymorphisms, *TaqI* (rs731236), *BsmI* (rs1544410) and rs2544038 showed a decrease in odds of breast cancer (TT vs. CC, OR: 0.74, 95% CI: 0.56–0.98, $p_{\text{trend}}=0.01$; GG vs. AA, OR: 0.74, 95% CI: 0.55–1.00, $p_{\text{trend}}=0.03$; TT vs. CC, OR: 0.74, 95% CI: 0.57–0.97, $p_{\text{trend}}=0.03$, respectively). For the remaining polymorphisms, associations with breast cancer were weak and confidence intervals included the null value. Once we adjusted for multiple comparisons, none of the SNP-breast cancer risk p-values were <0.002 , the threshold determined using the Bonferroni correction.

As presented in Table 3, we observed little or no heterogeneity in the association between vitamin-D related SNPs and breast cancer across tumor characteristics of the first primary breast cancer, with a few exceptions. For *VDR* rs2408876, there was a 42% decreased breast cancer risk among patients either ER+ or PR+ tumors as compared to women with ER–/PR– tumors (ROR: 0.59, 95% CI: 0.36–0.98). We also examined heterogeneity between ER+/PR– and ER–/PR– tumors and found similar variations in the RORs, with attenuation of most of the ORs (Supplemental Table 1). Other SNPs showed apparent variability across tumor subtypes, but the confidence intervals for the measure of heterogeneity included the null value.

We noted effect modification on a multiplicative scale ($p = 0.05$) for *CYP24A1* polymorphism rs927650. Women homozygous for the common allele of *CYP24A1* rs927650 who had plasma 25(OH)D of ≥ 19.1 ng/mL had reduced breast cancer risk compared to women with plasma 25(OH)D <19.1 ng/mL (OR: 0.43, 95% CI: 0.27–0.68; Supplemental Table 2). With adjustment for multiple comparisons, none of the interaction p-values were below the Bonferroni-determined threshold. Our findings however, were based on small numbers of women and therefore should be interpreted with caution. In analyses restricted to postmenopausal women the interaction for *CYP24A1* (rs927650) was no longer significant (Supplemental Table 3).

Discussion

In this population-based case-control study, we observed reduced risks for breast cancer in association with select biologically plausible vitamin D-related gene polymorphisms, particularly *CYP24A1*. Specifically, we observed potential 72% and 46% reductions for breast cancer risk in association with the homozygous minor allele genotype for *CYP24A1* polymorphism rs6068816 and rs13038432. After accounting for multiple comparisons, however, we found no interactions between *CYP24A1* and *GC* polymorphisms and plasma 25(OH)D. To our knowledge, this is the first study to examine effect modification of breast cancer risk by plasma 25(OH)D among vitamin D-related gene polymorphisms other than *VDR*.

CYP24A1 is located on chromosome 20 (Figure 1b) and plays an important role in vitamin D metabolism, specifically regulating the level of active vitamin D [27]. *CYP24A1* is amplified

in breast tumors, which may nullify growth control [48]. Two previous studies found no association between *CYP24A1* polymorphisms (rs2296241, rs2181874, rs4809958 and rs601305) and breast cancer risk [25,28] and another study found an increased risk with one polymorphism (rs6091822) and a decreased risk with two other *CYP24A1* polymorphisms (rs8124792 and rs6097809) [29]. We found decreased breast cancer risk for two *CYP24A1* polymorphisms that were not examined in these previous studies, rs13038432 and rs6068816.

In our study, there was a potential interaction between *CYP24A1* polymorphism rs927650 and plasma 25(OH)D; breast cancer risk was reduced among women with the homozygous common allele with plasma 25(OH)D ≥ 19.1 ng/mL compared to those with 25(OH)D < 19.1 ng/mL. A recent genome-wide association study (GWAS) demonstrated that variation in *CYP24A1* was related to circulating levels of 25(OH)D [49]. *CYP24A1* encodes 24-hydroxylase, which degrades 1,25(OH)₂D, reducing the growth control of 1,25(OH)₂D and potentially increasing breast cancer risk among women with certain *CYP24A1* polymorphisms [27]. We did not test for rs6013897, which has been highlighted in a recent GWAS study [49] as associated with vitamin D insufficiency. To our knowledge no previous publication has examined linkage disequilibrium between rs6013897 and any *CYP24A1* polymorphisms. Our findings appear to be compatible with the known function of *CYP24A1*, which suggests that the association with breast cancer may be modified through 25(OH)D.

We also found potential breast cancer risk reductions for a number of *VDR* polymorphisms, including *BsmI* (rs1544410), *TaqI* (rs731236), and rs2544038. It is interesting to note, all the *VDR* polymorphisms associated with decreased breast cancer risk or plasma 25(OH)D in our study were closer to the 3' end of the promoter region and part of block B (Figure 1a) [50]. The functionality of these *VDR* polymorphisms is not completely understood [51]. The *TaqI* (rs731236) polymorphism is on block B and part of the ligand-binding domain [27]. Our findings of a reduced risk comparing CC vs. TT in *TaqI* are consistent with the magnitude of effect observed in previous studies [52,35]. However, a few other studies have found an increased risk or no association, but these studies were composed of slightly different populations, either premenopausal women only or women in other countries with differing sun exposure [53,54]. Our findings of a reduced risk with *BsmI* are consistent with one previous study among white women [17], and two other studies [55,56] conducted within populations of different racial backgrounds. However, other studies conducted within white populations showed an increased breast cancer risk with *BsmI* [57,58,33,34,59]. We know of only one study that also assessed rs2544038, which found a slightly increased breast cancer risk with the CC vs. TT genotype [60].

Among *VDR* polymorphisms associated with increased risk, one SNP has not been previously published in relation to breast cancer, rs2239182. Our study showed *Apal* was associated with an increased breast cancer risk, which is consistent with three previous studies [53,61,62] and inconsistent with three others [56,52,25]. It is unclear if *Apal* is associated with increased breast cancer risk or if these are chance findings.

Within the vitamin D-binding protein encoded by *GC*, we examined two relatively common SNPs, rs7041 and rs4588 (Figure 1c). Previous breast cancer studies have found varied results [25,28]. In our population, we observed weak increases in breast cancer risk, with confidence intervals that included the null value, for both of these polymorphisms. Our breast cancer risk estimates were similar for rs7041 to two recent studies [25,28] and similar in rs4588 to one of these studies [25]. However, two other studies found a decreased breast cancer risk for rs7041 [63,64], only one examined rs4588 and also found an inverse association [63]. For both rs7041 and rs4588, we observed some variation in plasma 25(OH)D levels across genotype. Overall, our findings are in agreement with a recent study that showed *GC* variation is associated with 25(OH)D concentrations [65]. However, a GWAS study showed only *GC* rs2282679 was associated with vitamin D insufficiency, and thus variation in 25(OH)D across genotype may be influenced by other mechanisms [49].

These results support the concept that breast carcinogenesis may be influenced by the vitamin D axis, including the interaction between the different components of vitamin D, which includes circulating vitamin D, the *VDR* and the vitamin D-binding protein [66]. Few previous studies have assessed interactions between circulating 25(OH)D and vitamin D polymorphisms on breast cancer risk [33–35,63].

We acknowledge the following limitations of our study. First, we used a biologically based approach for SNP selection [67–69], however, with adjustments for multiple comparisons, none of the associations we observed met the conservative Bonferroni-threshold for significance. Thus, our results could be due to chance. Second, given that blood was collected near diagnosis and that 25(OH)D has a relatively short half-life of approximately 2–3 weeks [70], circulating vitamin D levels at the time of diagnosis may not reflect the etiologically relevant window timeframe. Third, we limited our analyses to white women, given genotypes in *VDR* have been shown to vary by race and ethnicity [71]. This may limit generalizability of our findings; however, our homogenous population is also a study strength, because there is less genetic variability. Fourth, our results are based on a small number of case subjects with the homozygous minor allele. It is unclear if our findings would be replicated in a larger study with more women with the homozygous minor alleles in *CYP24A1* gene.

Our study improves upon previous studies in a number of different ways. First, we examined a number of biologically plausible polymorphisms, not just those on *VDR*. Our results show that other vitamin D-related genes – particularly *CYP24A1* – may also be important in understanding the relationship between vitamin D and breast cancer risk. Second, our study is based on incident breast cancer cases. Vitamin D levels can also be affected by treatment [72–74] and changes in lifestyles behaviors after diagnosis with breast cancer. Blood samples in our population were collected prior to treatment with chemotherapy in 70% of the cases. Third, our study was population-based, reducing the likelihood of unquantified selection biases that are inherent in using select populations. As previously reported [37], LIBCSP participants for whom blood samples were available were more likely to be younger, report their race as white, to ever use alcohol, ever used hormone replacement, breast fed for more than 6 months, ever had a mammogram, and less likely to be past smokers. However, all statistical analyses included the frequency matching factor age, were

limited to whites only, and adjusted for ever having a mammogram, which may have helped to limit some of the potential selection bias associated with these differences. In addition, alcohol use, hormone replacement use, breastfeeding, and smoking were not confounders in our analyses. Further, our incidence density sampling approach improves our ability for estimating rate ratios, which enhances interpretation of our findings.

In conclusion, in our population-based study, breast cancer risk was associated with specific vitamin D-related SNPs, supporting the biologic plausibility of a relationship between vitamin D and breast cancer risk. Prospective studies evaluating 25(OH)D and breast cancer risk have had mixed results, some studies found 25(OH)D decreases breast cancer risk [19,20,24], whereas others reported no association [21–23]. We observed that the inverse association with vitamin D may be stronger among women with polymorphisms within *CYP24A1*. Genetic variation in the vitamin D pathway, specifically in *CYP24A1*, is potentially important to breast cancer risk, which should be considered when designing potential intervention strategies with vitamin D supplementation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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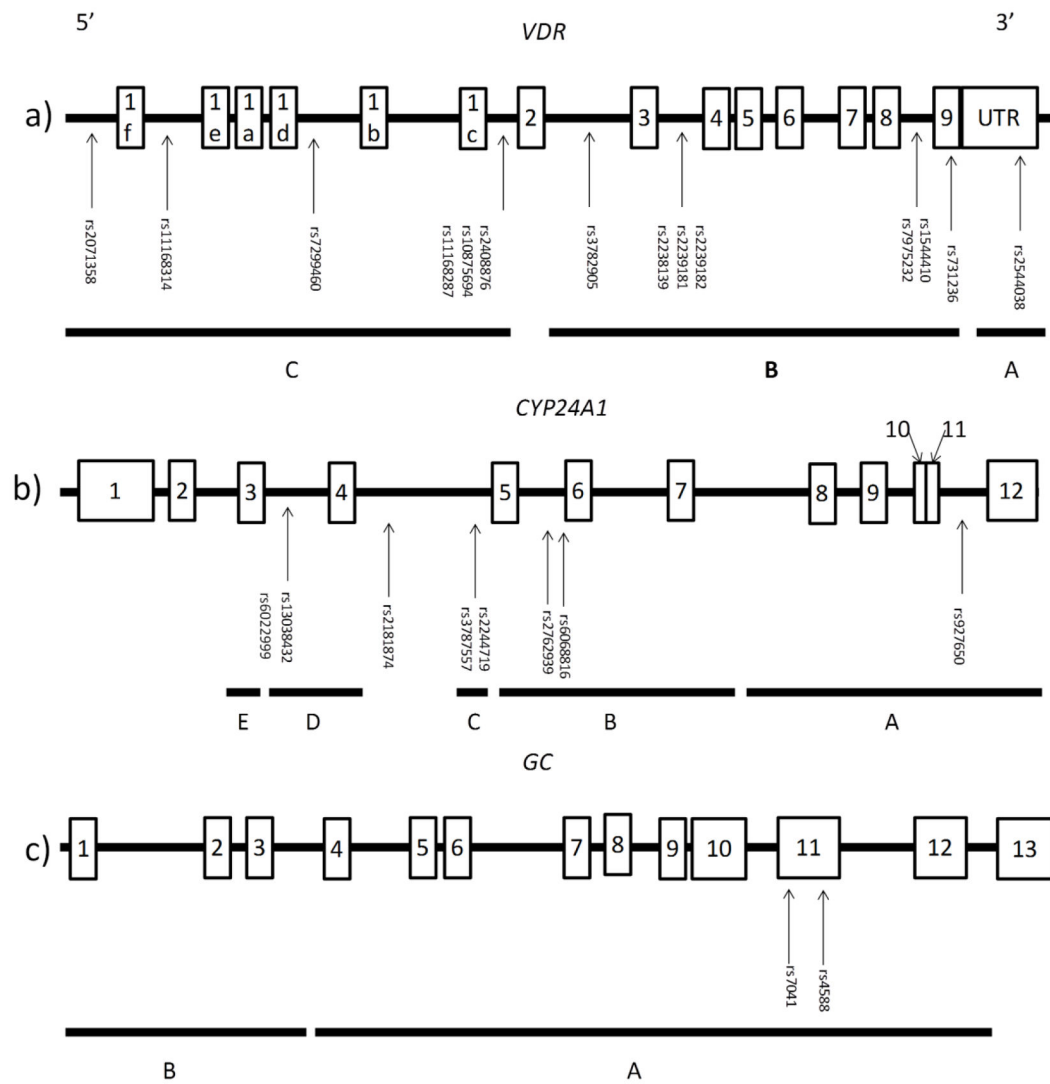


Figure 1. Position of vitamin D related gene polymorphisms use for analysis within each gene, a) *VDR* gene block and exon structure, individual SNPs are indicated with an arrow, b) *CYP24A1* gene, and c) *GC* gene. Exons are indicated by a square with the exon number in the middle.

Geometric Mean (95% CI) plasma 25(OH)D concentrations (ng/mL) by polymorphisms in the vitamin D receptor gene among white control participants (n=993), Long Island Breast Cancer Study Project (LIBCSP), 1996–1997

Table 1

Polymorphism	Homozygous common allele	Heterozygous	Homozygous minor allele	Heterozygous + Homozygous minor allele	p-value ^a	p-value ^b
VDR (<i>BsmI</i> , rs1544410)	AA: 27.0 (25.5–28.6)	AG: 27.1 (25.7–28.6)	GG: 26.6 (24.5–28.9)	AG+GG: 27.0 (25.8–28.2)	0.93	0.85
VDR (rs2071358)	CC: 26.4 (25.4–27.5)	CA: 28.2 (26.4–30.2)	AA: 24.5 (20.3–29.5)	CA+AA: 27.8 (26.1–29.6)	0.06	0.15
VDR (rs2239181)	AA: 26.8 (25.8–27.8)	AC: 27.0 (25.0–29.2)	CC: 26.7 (18.9–37.7)	AC+CC: 27.0 (25.1–29.1)	0.97	0.97
VDR (rs2239182)	GG: 26.6 (24.9–28.4)	GA: 26.7 (25.6–27.9)	AA: 27.6 (25.8–29.6)	GA+AA: 27.0 (26.0–28.0)	0.98	0.84
VDR (rs2408876)	TT: 28.4 (26.8–30.1)	TC: 25.9 (24.7–27.1)	CC: 26.7 (24.7–28.7)	TC+CC: 26.1 (25.0–27.1)	0.03	0.01
VDR (rs2544038)	TT: 27.5 (25.9–29.2)	TC: 26.2 (25.0–27.5)	CC: 27.5 (25.7–29.6)	TC+CC: 26.6 (25.5–27.7)	0.19	0.57
VDR (rs3782905)	GG: 26.3 (25.0–27.7)	GC: 27.4 (26.1–28.8)	CC: 27.6 (25.1–20.3)	GC+CC: 27.5 (26.3–28.7)	0.18	0.17
VDR (rs7299460)	CC: 27.1 (25.8–28.5)	CT: 26.9 (25.6–28.3)	TT: 26.3 (23.7–29.1)	CT+TT: 26.8 (25.6–28.0)	0.69	0.92
VDR (<i>TaqI</i> , rs731236)	CC: 27.2 (25.7–28.7)	CT: 26.8 (25.5–28.1)	TT: 26.5 (24.6–28.6)	CT+TT: 26.7 (25.6–27.9)	0.98	0.93
VDR (<i>ApaI</i> , rs7975232)	AA: 26.2 (24.6–27.8)	AC: 27.0 (25.8–28.3)	CC: 27.8 (25.9–29.9)	AC+CC: 27.3 (26.2–28.3)	0.84	0.70
VDR (rs10875694)	TT: 27.0 (26.0–28.2)	TA: 26.5 (25.0–28.2)	AA: 25.6 (21.7–30.2)	TA+AA: 26.4 (25.0–28.0)	0.54	0.45
VDR (rs11168287)	TT: 27.3 (25.6–29.1)	TC: 26.6 (25.4–27.9)	CC: 26.9 (25.3–28.6)	TC+CC: 26.7 (25.7–27.8)	0.78	0.54
VDR (rs11168314)	CC: 26.8 (25.7–28.0)	CT: 26.8 (25.3–28.4)	TT: 27.3 (22.6–32.9)	CT+TT: 26.9 (25.4–28.4)	0.88	0.65
CYP24A1 (rs927650)	CC: 27.0 (25.6–28.6)	CT: 27.0 (25.7–28.2)	TT: 26.3 (24.2–28.5)	CT+TT: 26.7 (25.7–27.9)	0.77	0.59
CYP24A1 (rs2181874)	GG: 27.2 (26.0–28.4)	GA: 26.5 (25.2–28.0)	AA: 26.0 (23.1–29.3)	GA+AA: 26.5 (25.2–27.7)	0.74	0.44
CYP24A1 (rs2244719)	TT: 26.8 (25.3–28.4)	TC: 26.8 (25.6–28.1)	CC: 27.3 (25.3–29.4)	TC+CC: 26.9 (25.9–28.0)	0.87	0.75
CYP24A1 (rs2585428)	GG: 26.0 (24.2–27.9)	GA: 27.7 (26.5–29.0)	AA: 26.5 (25.0–28.1)	GA+AA: 27.3 (26.3–28.3)	0.84	0.59
CYP24A1 (rs2762939)	TT: 27.5 (26.3–28.7)	TC: 25.9 (24.6–27.4)	CC: 27.0 (23.7–30.7)	TC+CC: 26.1 (24.8–27.4)	0.75	0.47
CYP24A1 (rs3787557)	TT: 26.6 (25.6–27.7)	TC: 27.4 (25.7–29.2)	CC: 26.8 (22.2–32.3)	TC+CC: 27.4 (25.8–29.1)	0.54	0.27
CYP24A1 (rs4809960)	TT: 26.5 (25.3–27.7)	TC: 27.8 (26.4–29.3)	CC: 25.4 (22.9–28.2)	TC+CC: 27.4 (26.2–28.7)	0.28	0.52
CYP24A1 (rs6022999)	AA: 27.4 (26.2–28.6)	AG: 26.5 (25.2–27.9)	GG: 26.0 (23.0–29.3)	AG+GG: 26.4 (25.2–27.7)	0.43	0.25
CYP24A1 (rs6068816)	CC: 26.8 (25.9–27.8)	CT: 27.2 (25.0–29.5)	TT: 24.7 (19.4–31.6)	CT+TT: 27.0 (25.0–29.2)	0.96	0.94
CYP24A1 (rs13038432)	AA: 27.0 (26.1–28.0)	AG: 26.3 (23.9–29.0)	GG: 23.3 (15.5–35.0)	AG+GG: 26.2 (23.8–28.8)	0.64	0.84
GC (rs4588)	CC: 28.3 (27.1–29.5)	CA: 25.5 (24.1–26.9)	AA: 24.7 (22.2–27.6)	CA+AA: 25.4 (24.2–26.6)	0.001	0.0004
GC (rs7041)	GG: 29.2 (27.6–30.9)	GT: 26.3 (25.0–27.6)	TT: 24.7 (22.9–26.6)	GT+TT: 25.8 (24.8–26.9)	0.001	0.001

^aComparing across all three genotypes, adjusted for season of blood draw, age, family history, and mammography use.

^bComparing homozygous major genotype to the combination of heterozygous and homozygous minor genotypes, adjusted for season of blood draw, age, family history, and mammography use.

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between breast cancer and polymorphisms in vitamin D-related genes, in white Long Island Breast Cancer Study Project participants (LIBCSP, 1996–1997)

Table 2

Gene (rs)	Genotype	Cases (N=967)	Controls (N=993)	Age-Adjusted OR (95% CI) ¹	Multivariable-Adjusted OR (95% CI) ²	P _{trend}
VDR (<i>TaqI</i> , rs731236)	CC (tt)	383	345	1.0	1.0	0.01
	CT (Tt)	428	479	0.80 (0.66–0.98)	0.79 (0.64–0.96)	
	TT (TT)	141	168	0.76 (0.58–1.00)	0.74 (0.56–0.98)	
	CT+TT	569	647	0.79 (0.66–0.96)	0.77 (0.64–0.94)	
VDR (<i>BsmI</i> , rs1544410)	AA (BB)	337	318	1.0	1.0	0.03
	AG (Bb)	385	432	0.84 (0.68–1.03)	0.82 (0.66–1.01)	
	GG (bb)	120	149	0.77 (0.58–1.03)	0.74 (0.55–1.00)	
	AG+GG	505	581	0.82 (0.67–1.00)	0.80 (0.65–0.98)	
VDR (rs2544038)	TT	322	296	1.0	1.0	0.03
	TC	458	488	0.89 (0.72–1.09)	0.89 (0.72–1.10)	
	CC	163	198	0.75 (0.58–0.98)	0.74 (0.57–0.97)	
	TC+CC	621	686	0.85 (0.70–1.03)	0.85 (0.69–1.04)	
VDR (rs7299460)	CC	445	424	1.0	1.0	0.11
	CT	420	453	0.90 (0.74–1.08)	0.92 (0.76–1.12)	
	TT	86	115	0.74 (0.54–1.01)	0.77 (0.56–1.06)	
	CT+TT	506	568	0.86 (0.72–1.04)	0.89 (0.74–1.07)	
VDR (rs3782905)	GG	422	447	1.0	1.0	0.77
	GC	421	391	1.16 (0.96–1.41)	1.16 (0.95–1.42)	
	CC	86	112	0.83 (0.61–1.14)	0.80 (0.57–1.10)	
	GC+CC	507	503	1.09 (0.91–1.31)	1.08 (0.89–1.30)	
VDR (rs10875694)	TT	631	647	1.0	1.0	0.44
	TA	293	307	0.98 (0.81–1.20)	0.95 (0.78–1.17)	
	AA	23	30	0.79 (0.45–1.38)	0.80 (0.46–1.42)	
	TA+AA	316	337	0.96 (0.80–1.17)	0.94 (0.77–1.14)	
VDR (rs2071358)	CC	637	699	1.0	1.0	0.25
	CA	284	260	1.17 (0.96–1.43)	1.18 (0.96–1.45)	
	AA	25	29	1.00 (0.57–1.73)	0.97 (0.56–1.71)	

Gene (rs)	Genotype	Cases (N=967)	Controls (N=993)	Age-Adjusted OR (95% CI) ¹	Multivariable-Adjusted OR (95% CI) ²	P _{trend}
VDR (rs11168287)	CA+AA	309	289	1.15 (0.95–1.40)	1.16 (0.95–1.42)	1.0
	TT	221	241	1.0	1.0	0.97
	TC	487	480	1.14 (0.91–1.42)	1.10 (0.87–1.39)	
	CC	237	258	1.03 (0.80–1.33)	1.01 (0.77–1.32)	
VDR (rs2408876)	TC+CC	724	738	1.10 (0.89–1.36)	1.07 (0.86–1.33)	
	TT	328	328	1.0	1.0	0.86
	TC	449	497	0.91 (0.74–1.11)	0.91 (0.74–1.12)	
	CC	166	166	1.04 (0.80–1.37)	1.01 (0.77–1.33)	
VDR (rs2239181)	TC+CC	615	663	0.94 (0.78–1.14)	0.93 (0.77–1.14)	
	AA	737	775	1.0	1.0	0.89
	AC	198	197	1.03 (0.83–1.29)	1.01 (0.80–1.27)	
	CC	13	13	1.05 (0.48–2.29)	1.08 (0.49–2.38)	
VDR (rs11168314)	AC+CC	211	210	1.03 (0.83–1.29)	1.01 (0.81–1.27)	
	CC	597	600	1.0	1.0	0.57
	CT	302	347	0.89 (0.73–1.08)	0.89 (0.73–1.09)	
	TT	43	40	1.13 (0.72–1.77)	1.11 (0.70–1.76)	
VDR (rs2239182)	CT+TT	345	387	0.91 (0.76–1.10)	0.91 (0.75–1.11)	
	GG	232	250	1.0	1.0	0.25
	GA	468	513	0.95 (0.76–1.19)	0.96 (0.77–1.21)	
	AA	250	226	1.15 (0.89–1.49)	1.17 (0.90–1.53)	
VDR (Apat, rs7975232)	GA+AA	718	739	1.01 (0.82–1.25)	1.03 (0.83–1.27)	
	AA (AA)	271	313	1.0	1.0	0.09
	AC (Aa)	473	476	1.14 (0.93–1.41)	1.17 (0.94–1.45)	
	CC (aa)	204	199	1.18 (0.91–1.52)	1.24 (0.95–1.62)	
CYP24A1 (rs6068816)	AC+CC	677	675	1.15 (0.95–1.40)	1.19 (0.97–1.46)	
	CC	778	784	1.0	1.0	0.01
	CT	164	189	0.88 (0.70–1.12)	0.82 (0.65–1.05)	
	TT	6	17	0.36 (0.14–0.93)	0.28 (0.10–0.76)	
CYP24A1 (rs13038432)	CT+TT	170	206	0.84 (0.67–1.06)	0.77 (0.61–0.98)	
	AA	830	835	1.0	1.0	0.02
	AG	113	148	0.78 (0.60–1.01)	0.74 (0.57–0.98)	

Gene (rs)	Genotype	Cases (N=967)	Controls (N=993)	Age-Adjusted OR (95% CI) ¹	Multivariable-Adjusted OR (95% CI) ²	P _{trend}
	GG	5	8	0.60 (0.19–1.84)	0.54 (0.17–1.67)	
	AG+GG	118	156	0.77 (0.59–1.00)	0.73 (0.56–0.96)	
<i>CYP24A1</i> (rs2244719)	TT	287	304	1.0	1.0	0.98
	TC	463	461	1.08 (0.87–1.33)	1.11 (0.90–1.38)	
	CC	194	222	0.93 (0.72–1.20)	0.98 (0.76–1.28)	
	TC+CC	657	683	1.03 (0.85–1.25)	1.07 (0.88–1.31)	
<i>CYP24A1</i> (rs2585428)	GG	264	261	1.0	1.0	0.88
	GA	442	487	0.89 (0.72–1.10)	0.90 (0.72–1.12)	
	AA	243	243	0.94 (0.73–1.21)	0.99 (0.76–1.28)	
	GA+AA	685	730	0.91 (0.74–1.11)	0.93 (0.75–1.14)	
<i>CYP24A1</i> (rs927650)	CC	274	296	1.0	1.0	0.66
	CT	462	471	1.09 (0.88–1.35)	1.11 (0.90–1.39)	
	TT	207	220	1.04 (0.80–1.34)	1.05 (0.81–1.36)	
	CT+TT	669	691	1.07 (0.88–1.31)	1.09 (0.89–1.34)	
<i>CYP24A1</i> (rs4809960)	TT	522	512	1.0	1.0	0.33
	TC	342	395	0.83 (0.68–1.00)	0.81 (0.67–0.99)	
	CC	84	82	1.04 (0.75–1.46)	1.06 (0.75–1.50)	
	TC+CC	426	477	0.86 (0.72–1.03)	0.85 (0.71–1.03)	
<i>CYP24A1</i> (rs2762939)	TT	514	560	1.0	1.0	0.51
	TC	348	353	1.07 (0.88–1.29)	1.07 (0.87–1.30)	
	CC	59	57	1.07 (0.72–1.58)	1.09 (0.73–1.63)	
	TC+CC	407	410	1.07 (0.89–1.28)	1.07 (0.88–1.29)	
<i>CYP24A1</i> (rs6022999)	AA	494	554	1.0	1.0	0.11
	AG	366	361	1.11 (0.92–1.35)	1.10 (0.90–1.34)	
	GG	86	73	1.33 (0.94–1.87)	1.32 (0.93–1.87)	
	AG+GG	452	434	1.15 (0.96–1.38)	1.13 (0.94–1.37)	
<i>CYP24A1</i> (rs2181874)	GG	508	560	1.0	1.0	0.11
	GA	359	366	1.09 (0.90–1.32)	1.10 (0.90–1.34)	
	AA	79	66	1.36 (0.96–1.93)	1.32 (0.92–1.89)	
	GA+AA	438	432	1.13 (0.94–1.35)	1.14 (0.94–1.37)	
<i>CYP24A1</i> (rs3787557)	TT	685	725	1.0	1.0	0.49

Gene (rs)	Genotype	Cases (N=967)	Controls (N=993)	Age-Adjusted OR (95% CI) ¹	Multivariable-Adjusted OR (95% CI) ²	P _{trend}
GC (rs7041)	TC	238	238	1.05 (0.85–1.29)	1.03 (0.83–1.28)	
	CC	25	24	1.14 (0.63–2.04)	1.34 (0.73–2.46)	
	TC+CC	263	262	1.05 (0.86–1.29)	1.05 (0.85–1.30)	
	GG	281	311	1.0	1.0	0.77
	GT	470	474	1.07 (0.87–1.32)	1.09 (0.88–1.35)	
GC (rs4588)	TT	186	193	1.05 (0.81–1.37)	1.02 (0.78–1.34)	
	GT+TT	656	667	1.06 (0.87–1.30)	1.07 (0.87–1.31)	
	CC	456	514	1.0	1.0	0.43
	CA	402	393	1.12 (0.93–1.36)	1.11 (0.92–1.35)	
	AA	82	84	1.06 (0.76–1.48)	1.05 (0.75–1.48)	
	CA+AA	484	477	1.11 (0.93–1.33)	1.10 (0.92–1.33)	

¹ age-adjusted

² adjusted for age, first degree family history of breast cancer, and mammography use

Table 3

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between vitamin D-related polymorphisms and breast cancer as defined by stage and hormone receptor status, in white participants of the Long Island Breast Cancer Study Project, 1996–1997

Polymorphism	Genotype	Controls (N=993)		In Situ		Invasive		Ratio of ORs ²		Hormone Receptor Status			
		N	OR (95% CI) ¹	N	OR (95% CI) ¹	N	OR (95% CI) ¹	N	OR (95% CI) ¹	ER-/PR-	ER+/PR-	ER+ and/or PR+	Ratio of ORs ³
VDR (rs2071358)	CC	699	1.0	516	1.0	1.0	1.0	26	1.0	1.0	116	1.0	1.0
	CA	260	0.91 (0.61–1.36)	245	1.24 (1.00–1.55)	1.36 (0.91–2.03)	52	1.08 (0.65–1.80)	253	1.12 (0.85–1.49)	1.04 (0.61–1.77)		
	AA	29	1.49 (0.63–3.53)	18	0.85 (0.46–1.58)	0.57 (0.23–1.42)	29	1.07 (0.60–1.90)	123	1.01 (0.73–1.40)	0.95 (0.52–1.74)		
VDR (BsmI, rs1544410)	CA+AA	289	0.97 (0.67–1.41)	263	1.20 (0.97–1.49)	1.24 (0.85–1.81)	81	1.08 (0.67–1.74)	376	1.08 (0.83–1.41)	1.01 (0.61–1.66)		
	AA	318	1.0	285	1.0	1.0	47	1.0	173	1.0	1.0		
	AG	432	0.91 (0.61–1.36)	319	0.80 (0.64–1.00)	0.88 (0.59–1.33)	36	0.55 (0.34–0.88)	207	0.87 (0.67–1.12)	1.58 (0.97–2.59)		
VDR (TaqI, rs731236)	GG	149	1.10 (0.65–1.85)	93	0.67 (0.49–0.93)	0.61 (0.36–1.05)	14	0.58 (0.30–1.12)	59	0.70 (0.48–1.02)	1.21 (0.60–2.43)		
	AG+GG	581	0.96 (0.66–1.40)	412	0.77 (0.62–0.95)	0.80 (0.55–1.18)	50	0.56 (0.36–0.86)	266	0.82 (0.64–1.05)	1.48 (0.94–2.34)		
	CC	345	1.0	321	1.0	1.0	49	1.0	201	1.0	1.0		
VDR (rs2239181)	CT	479	0.81 (0.56–1.19)	355	0.78 (0.63–0.97)	0.96 (0.65–1.40)	42	0.61 (0.39–0.95)	224	0.78 (0.61–1.00)	1.28 (0.81–2.05)		
	TT	168	1.04 (0.64–1.67)	109	0.68 (0.50–0.91)	0.66 (0.40–1.07)	18	0.72 (0.40–1.29)	69	0.68 (0.48–0.96)	0.95 (0.51–1.78)		
	CT+TT	647	0.87 (0.61–1.24)	464	0.75 (0.62–0.92)	0.86 (0.61–1.23)	60	0.64 (0.42–0.96)	293	0.76 (0.60–0.95)	1.19 (0.77–1.82)		
VDR (rs2408876)	AA	775	1.0	603	1.0	1.0	81	1.0	391	1.0	1.0		
	AC	197	0.81 (0.52–1.27)	168	1.05 (0.83–1.34)	1.29 (0.83–2.03)	26	1.27 (0.78–2.05)	95	0.90 (0.68–1.20)	0.71 (0.43–1.19)		
	CC	13	1.34 (0.37–4.86)	10	1.02 (0.43–2.38)	0.76 (0.20–2.83)	0	0 (0–)	6	1.05 (0.38–2.85)	NE		
VDR (rs7299460)	AC+CC	210	0.85 (0.55–1.30)	178	1.05 (0.83–1.33)	1.24 (0.81–1.91)	26	1.18 (0.73–1.91)	101	0.91 (0.69–1.20)	0.77 (0.46–1.28)		
	TT	328	1.0	278	1.0	1.0	28	1.0	179	1.0	1.0		
	TC	497	0.86 (0.61–1.13)	363	0.87 (0.70–1.08)	0.78 (0.53–1.16)	61	1.43 (0.89–2.32)	232	0.85 (0.66–1.10)	0.59 (0.36–0.98)		
VDR (rs7299460)	CC	166	1.10 (0.66–1.84)	135	0.99 (0.74–1.33)	0.90 (0.54–1.51)	17	1.22 (0.64–2.32)	80	0.94 (0.67–1.31)	0.77 (0.39–1.50)		
	TC+CC	663	1.11 (0.77–1.60)	498	0.90 (0.73–1.10)	0.81 (0.56–1.18)	78	1.38 (0.87–2.20)	312	0.87 (0.69–1.11)	0.63 (0.39–1.02)		
	CC	424	1.0	368	1.0	1.0	57	1.0	223	1.0	1.0		
VDR (rs7299460)	CT	453	0.98 (0.69–1.40)	345	0.91 (0.74–1.12)	0.93 (0.65–1.33)	40	0.65 (0.42–1.02)	228	1.02 (0.80–1.29)	1.55 (0.98–2.46)		
	TT	115	0.80 (0.44–1.46)	71	0.76 (0.54–1.07)	0.95 (0.51–1.76)	12	0.75 (0.38–1.47)	44	0.80 (0.54–1.20)	1.07 (0.53–2.18)		
	CT+TT	568	0.94 (0.67–1.33)	416	0.88 (0.72–1.07)	0.93 (0.66–1.32)	52	0.68 (0.45–1.02)	272	0.97 (0.78–1.22)	1.44 (0.94–2.21)		

Polymorphism	Genotype	Stage												Hormone Receptor Status					
		In Situ				Invasive				Ratio of ORs ²				ER-/PR-		ER+ and/or PR+		Ratio of ORs ³	
		N	OR (95% CI) ¹	N	OR (95% CI) ¹	N	OR (95% CI) ¹	N	OR (95% CI) ¹	OR (95% CI) ¹	OR (95% CI) ¹	N	OR (95% CI) ¹	N	OR (95% CI) ¹	N	OR (95% CI) ¹	OR (95% CI) ¹	OR (95% CI) ¹
VDR (rs10875694)	TT	647	1.0	522	1.0	65	1.0	337	1.0	337	1.0	1.0	337	1.0	337	1.0	1.0	1.0	
	TA	307	1.00 (0.69-1.43)	237	0.94 (0.76-1.17)	42	0.94 (0.65-1.36)	42	1.34 (0.87-2.04)	142	0.88 (0.68-1.12)	142	0.88 (0.68-1.12)	142	0.88 (0.68-1.12)	142	0.88 (0.68-1.12)	0.66 (0.42-1.02)	0.66 (0.42-1.02)
	AA	30	NE	23	0.98 (0.56-1.74)	NE	2	0.70 (0.16-3.02)	13	0.85 (0.43-1.69)	13	0.85 (0.43-1.69)	13	0.85 (0.43-1.69)	13	0.85 (0.43-1.69)	1.22 (0.27-5.61)	1.22 (0.27-5.61)	
VDR (rs2544038)	TA+AA	337	0.91 (0.64-1.31)	260	0.94 (0.77-1.16)	44	1.04 (0.72-1.50)	155	0.87 (0.69-1.11)	155	0.87 (0.69-1.11)	155	0.87 (0.69-1.11)	155	0.87 (0.69-1.11)	155	0.87 (0.69-1.11)	0.68 (0.44-1.06)	0.68 (0.44-1.06)
	TT	296	1.0	263	1.0	36	1.0	163	1.0	163	1.0	1.0	163	1.0	163	1.0	1.0	1.0	
	TC	488	0.88 (0.60-1.29)	377	0.89 (0.72-1.12)	52	1.02 (0.69-1.49)	243	0.95 (0.74-1.23)	243	0.95 (0.74-1.23)	243	0.95 (0.74-1.23)	243	0.95 (0.74-1.23)	243	0.95 (0.74-1.23)	1.04 (0.64-1.68)	1.04 (0.64-1.68)
VDR (rs2239182)	CC	198	0.68 (0.41-1.13)	137	0.75 (0.57-1.01)	19	1.11 (0.66-1.87)	82	0.71 (0.51-1.00)	82	0.71 (0.51-1.00)	82	0.71 (0.51-1.00)	82	0.71 (0.51-1.00)	82	0.71 (0.51-1.00)	0.91 (0.48-1.71)	0.91 (0.48-1.71)
	TC+CC	686	0.82 (0.57-1.18)	514	0.85 (0.69-1.05)	71	1.04 (0.72-1.49)	325	0.88 (0.69-1.12)	325	0.88 (0.69-1.12)	325	0.88 (0.69-1.12)	325	0.88 (0.69-1.12)	325	0.88 (0.69-1.12)	1.00 (0.63-1.58)	1.00 (0.63-1.58)
	GG	250	1.0	190	1.0	21	1.0	124	1.0	124	1.0	1.0	124	1.0	124	1.0	1.0	1.0	
VDR (rs11168314)	GA	513	1.04 (0.69-1.58)	381	0.95 (0.74-1.20)	53	0.91 (0.59-1.38)	236	0.88 (0.67-1.16)	236	0.88 (0.67-1.16)	236	0.88 (0.67-1.16)	236	0.88 (0.67-1.16)	236	0.88 (0.67-1.16)	0.72 (0.41-1.27)	0.72 (0.41-1.27)
	AA	226	1.06 (0.65-1.73)	213	1.19 (0.90-1.58)	35	1.13 (0.69-1.85)	133	1.12 (0.81-1.54)	133	1.12 (0.81-1.54)	133	1.12 (0.81-1.54)	133	1.12 (0.81-1.54)	133	1.12 (0.81-1.54)	0.61 (0.33-1.14)	0.61 (0.33-1.14)
	GA+AA	739	1.05 (0.71-1.55)	594	1.02 (0.81-1.28)	88	0.97 (0.65-1.45)	369	0.95 (0.74-1.24)	369	0.95 (0.74-1.24)	369	0.95 (0.74-1.24)	369	0.95 (0.74-1.24)	369	0.95 (0.74-1.24)	0.68 (0.40-1.16)	0.68 (0.40-1.16)
VDR (rs3782905)	CC	600	1.0	485	1.0	51	1.0	212	1.0	212	1.0	1.0	212	1.0	212	1.0	1.0	1.0	
	CT	347	0.76 (0.52-1.11)	257	0.92 (0.74-1.13)	48	1.21 (0.82-1.77)	115	1.00 (0.78-1.28)	115	1.00 (0.78-1.28)	115	1.00 (0.78-1.28)	115	1.00 (0.78-1.28)	115	1.00 (0.78-1.28)	1.07 (0.68-1.68)	1.07 (0.68-1.68)
	TT	40	0.99 (0.43-2.29)	36	1.14 (0.70-1.85)	8	1.16 (0.50-2.69)	63	0.91 (0.64-1.30)	63	0.91 (0.64-1.30)	63	0.91 (0.64-1.30)	63	0.91 (0.64-1.30)	63	0.91 (0.64-1.30)	1.85 (0.83-4.14)	1.85 (0.83-4.14)
VDR (rs11168287)	CT+TT	387	0.79 (0.55-1.13)	293	0.94 (0.77-1.15)	56	1.20 (0.83-1.73)	278	0.82 (0.55-1.24)	278	0.82 (0.55-1.24)	278	0.82 (0.55-1.24)	278	0.82 (0.55-1.24)	278	0.82 (0.55-1.24)	1.19 (0.77-1.83)	1.19 (0.77-1.83)
	GG	447	1.0	352	1.0	54	1.0	209	1.0	209	1.0	1.0	209	1.0	209	1.0	1.0	1.0	
	GC	391	1.21 (0.84-1.73)	344	1.15 (0.93-1.42)	48	0.95 (0.66-1.38)	218	1.24 (0.97-1.58)	218	1.24 (0.97-1.58)	218	1.24 (0.97-1.58)	218	1.24 (0.97-1.58)	218	1.24 (0.97-1.58)	1.19 (0.76-1.85)	1.19 (0.76-1.85)
VDR (rs11168287)	CC	112	0.68 (0.35-1.31)	73	0.82 (0.58-1.15)	7	1.20 (0.62-2.35)	55	1.07 (0.73-1.56)	55	1.07 (0.73-1.56)	55	1.07 (0.73-1.56)	55	1.07 (0.73-1.56)	55	1.07 (0.73-1.56)	1.99 (0.85-4.67)	1.99 (0.85-4.67)
	GC+CC	503	1.09 (0.77-1.54)	417	1.08 (0.88-1.31)	55	0.99 (0.70-1.41)	273	1.20 (0.95-1.51)	273	1.20 (0.95-1.51)	273	1.20 (0.95-1.51)	273	1.20 (0.95-1.51)	273	1.20 (0.95-1.51)	1.29 (0.84-1.99)	1.29 (0.84-1.99)
	TT	241	1.0	178	1.0	57	1.0	250	1.0	250	1.0	1.0	250	1.0	250	1.0	1.0	1.0	
VDR (ApaI, rs7975232)	TC	480	0.96 (0.63-1.44)	401	1.13 (0.89-1.45)	44	1.19 (0.78-1.80)	201	1.03 (0.81-1.31)	201	1.03 (0.81-1.31)	201	1.03 (0.81-1.31)	201	1.03 (0.81-1.31)	201	1.03 (0.81-1.31)	1.02 (0.65-1.60)	1.02 (0.65-1.60)
	CC	258	0.80 (0.49-1.30)	200	1.06 (0.80-1.41)	7	1.33 (0.81-2.18)	41	1.06 (0.69-1.62)	41	1.06 (0.69-1.62)	41	1.06 (0.69-1.62)	41	1.06 (0.69-1.62)	41	1.06 (0.69-1.62)	1.34 (0.56-3.20)	1.34 (0.56-3.20)
	TC+CC	738	0.90 (0.61-1.33)	601	1.11 (0.88-1.40)	51	1.23 (0.83-1.83)	242	1.03 (0.82-1.30)	242	1.03 (0.82-1.30)	242	1.03 (0.82-1.30)	242	1.03 (0.82-1.30)	242	1.03 (0.82-1.30)	1.06 (0.69-1.63)	1.06 (0.69-1.63)
VDR (rs11168287)	AA	313	1.0	213	1.0	30	1.0	129	1.0	129	1.0	1.0	129	1.0	129	1.0	1.0	1.0	
	AC	476	0.91 (0.62-1.34)	395	1.24 (0.99-1.56)	47	1.36 (0.92-2.01)	259	1.37 (1.05-1.79)	259	1.37 (1.05-1.79)	259	1.37 (1.05-1.79)	259	1.37 (1.05-1.79)	259	1.37 (1.05-1.79)	1.33 (0.79-2.23)	1.33 (0.79-2.23)
	CC	199	0.89 (0.54-1.45)	175	1.33 (1.01-1.76)	31	1.51 (0.92-2.48)	104	1.29 (0.93-1.79)	104	1.29 (0.93-1.79)	104	1.29 (0.93-1.79)	104	1.29 (0.93-1.79)	104	1.29 (0.93-1.79)	0.77 (0.43-1.37)	0.77 (0.43-1.37)
VDR (rs11168287)	AC+CC	675	0.90 (0.63-1.29)	570	1.27 (1.02-1.57)	78	1.40 (0.97-2.03)	363	1.34 (1.04-1.73)	363	1.34 (1.04-1.73)	363	1.34 (1.04-1.73)	363	1.34 (1.04-1.73)	363	1.34 (1.04-1.73)	1.10 (0.68-1.78)	1.10 (0.68-1.78)

Polymorphism	Genotype	Stage												Hormone Receptor Status					
		<i>In Situ</i>				Invasive				Ratio of ORs ²				ER-/PR-		ER+ and/or PR+		Ratio of ORs ³	
		N	OR (95% CI) ¹	N	OR (95% CI) ¹	N	OR (95% CI) ¹	N	OR (95% CI) ¹	OR (95% CI) ¹	OR (95% CI) ¹	N	OR (95% CI) ¹	N	OR (95% CI) ¹	N	OR (95% CI) ¹	OR (95% CI) ¹	OR (95% CI) ¹
CYP24A1 (rs13038432)	AA	835	1.0	680	1.0	99	1.0	99	1.0	425	1.0	425	1.0	1.0	1.0	1.0	1.0	1.0	
	AG	148	0.48 (0.26-0.88)	99	0.80 (0.60-1.07)	10	1.67 (0.91-3.07)	10	0.59 (0.30-1.16)	64	0.82 (0.59-1.14)	64	0.82 (0.59-1.14)	1.41 (0.69-2.86)					
	GG	8	1.14 (0.24-5.46)	3	0.39 (0.10-1.51)	0	0.34 (0.06-2.11)	0	0 (-)	4	0.82 (0.24-2.79)	4	0.82 (0.24-2.79)	NE					
CYP24A1 (rs6068816)	AG+GG	156	0.52 (0.30-0.92)	102	0.78 (0.59-1.03)	10	1.49 (0.84-2.65)	10	0.55 (0.28-1.09)	68	0.82 (0.60-1.13)	68	0.82 (0.60-1.13)	1.49 (0.73-3.02)					
	CC	784	1.0	644	1.0	88	1.0	88	1.0	405	1.0	405	1.0	1.0	1.0	1.0	1.0	1.0	
	CT	189	0.85 (0.55-1.33)	135	0.81 (0.63-1.05)	21	0.95 (0.61-1.50)	21	1.00 (0.60-1.66)	84	0.79 (0.59-1.06)	84	0.79 (0.59-1.06)	0.79 (0.46-1.36)					
CYP24A1 (rs4809960)	TT	17	0.60 (0.14-2.67)	3	0.20 (0.06-0.71)	0	0.34 (0.06-2.06)	0	NE	3	0.32 (0.09-1.12)	3	0.32 (0.09-1.12)	NE					
	CT+TT	206	0.83 (0.54-1.28)	138	0.76 (0.59-0.98)	21	0.91 (0.59-1.42)	21	0.92 (0.55-1.52)	87	0.75 (0.56-1.00)	87	0.75 (0.56-1.00)	0.82 (0.48-1.40)					
	TT	512	1.0	432	1.0	62	1.0	62	1.0	263	1.0	263	1.0	1.0	1.0	1.0	1.0	1.0	
CYP24A1 (rs3787557)	TC	395	0.76 (0.52-1.09)	285	0.82 (0.67-1.01)	39	1.09 (0.75-1.58)	39	0.81 (0.53-1.25)	184	0.87 (0.69-1.11)	184	0.87 (0.69-1.11)	1.08 (0.69-1.70)					
	CC	82	1.53 (0.87-2.69)	65	0.97 (0.67-1.40)	8	0.63 (0.36-1.12)	8	0.78 (0.34-1.78)	46	1.11 (0.73-1.68)	46	1.11 (0.73-1.68)	1.43 (0.61-3.37)					
	TC+CC	477	0.87 (0.62-1.23)	350	0.85 (0.69-1.03)	47	0.97 (0.69-1.37)	47	0.80 (0.53-1.21)	230	0.91 (0.73-1.14)	230	0.91 (0.73-1.14)	1.13 (0.74-1.74)					
CYP24A1 (rs6022999)	TT	725	1.0	569	1.0	77	1.0	77	1.0	352	1.0	352	1.0	1.0	1.0	1.0	1.0	1.0	
	TC	238	1.25 (0.85-1.83)	192	0.98 (0.78-1.24)	30	0.79 (0.53-1.16)	30	1.15 (0.73-1.82)	124	1.02 (0.78-1.33)	124	1.02 (0.78-1.33)	0.89 (0.55-1.44)					
	CC	24	1.70 (0.61-4.70)	20	1.27 (0.67-2.42)	3	0.75 (0.27-2.08)	3	1.42 (0.40-5.00)	14	1.36 (0.66-2.80)	14	1.36 (0.66-2.80)	0.96 (0.26-3.53)					
CYP24A1 (rs2244719)	TC+CC	262	1.28 (0.89-1.85)	212	1.00 (0.80-1.25)	33	0.78 (0.54-1.14)	33	1.17 (0.75-1.85)	138	1.05 (0.81-1.35)	138	1.05 (0.81-1.35)	0.90 (0.56-1.43)					
	AA	554	1.0	405	1.0	52	1.0	52	1.0	264	1.0	264	1.0	1.0	1.0	1.0	1.0	1.0	
	AG	361	0.95 (0.66-1.37)	305	1.13 (0.92-1.39)	45	1.19 (0.82-1.72)	45	1.25 (0.81-1.92)	185	1.08 (0.85-1.37)	185	1.08 (0.85-1.37)	0.86 (0.55-1.36)					
CYP24A1 (rs2585428)	GG	73	1.37 (0.75-2.53)	70	1.30 (0.90-1.89)	10	0.95 (0.51-1.75)	10	1.43 (0.67-3.07)	43	1.30 (0.85-2.00)	43	1.30 (0.85-2.00)	0.91 (0.41-2.01)					
	AG+GG	434	1.02 (0.73-1.43)	375	1.16 (0.95-1.41)	55	1.14 (0.80-1.61)	55	1.27 (0.85-1.92)	228	1.11 (0.89-1.40)	228	1.11 (0.89-1.40)	0.87 (0.57-1.34)					
	TT	304	1.0	234	1.0	36	1.0	36	1.0	139	1.0	139	1.0	1.0	1.0	1.0	1.0	1.0	
CYP24A1 (rs2585428)	TC	461	1.00 (0.67-1.47)	386	1.14 (0.91-1.43)	56	1.15 (0.77-1.71)	56	1.11 (0.70-1.75)	249	1.25 (0.96-1.63)	249	1.25 (0.96-1.63)	1.13 (0.69-1.83)					
	CC	222	1.00 (0.62-1.60)	158	0.98 (0.74-1.30)	17	0.99 (0.61-1.60)	17	0.70 (0.37-1.30)	100	1.05 (0.76-1.46)	100	1.05 (0.76-1.46)	1.51 (0.78-2.91)					
	TC+CC	683	1.00 (0.69-1.44)	544	1.09 (0.88-1.35)	73	1.09 (0.75-1.59)	73	0.98 (0.63-1.52)	349	1.19 (0.92-1.52)	349	1.19 (0.92-1.52)	1.21 (0.76-1.92)					
CYP24A1 (rs2585428)	GG	261	1.0	218	1.0	25	1.0	25	1.0	143	1.0	143	1.0	1.0	1.0	1.0	1.0	1.0	
	GA	487	0.95 (0.64-1.41)	358	0.89 (0.70-1.12)	58	0.93 (0.62-1.40)	58	1.19 (0.72-1.96)	223	0.85 (0.65-1.11)	223	0.85 (0.65-1.11)	0.71 (0.42-1.19)					
	AA	243	0.88 (0.54-1.43)	208	1.01 (0.77-1.32)	26	1.15 (0.70-1.87)	26	0.95 (0.52-1.74)	127	0.95 (0.70-1.30)	127	0.95 (0.70-1.30)	1.00 (0.53-1.87)					
GA+AA	730	0.93 (0.63-1.35)	566	0.93 (0.74-1.15)	84	1.00 (0.68-1.47)	84	1.11 (0.69-1.79)	350	0.88 (0.68-1.13)	350	0.88 (0.68-1.13)	0.79 (0.48-1.30)						

Polymorphism	Genotype	Stage												Hormone Receptor Status					
		In Situ				Invasive				Ratio of ORs ²				ER-/PR-		ER+ and/or PR+		Ratio of ORs ³	
		N	OR (95% CI) ¹	N	OR (95% CI) ¹	N	OR (95% CI) ¹	N	OR (95% CI) ¹	OR (95% CI) ¹	OR (95% CI) ¹	N	OR (95% CI) ¹	N	OR (95% CI) ¹	N	OR (95% CI) ¹	OR (95% CI) ¹	OR (95% CI) ¹
CYP24A1 (rs27650)	CC	296	51	1.0	223	1.0	223	1.0	31	1.0	31	1.0	139	1.0	139	1.0	1.0	1.0	
	CT	471	86	1.07 (0.73-1.59)	376	1.12 (0.89-1.41)	1.05 (0.70-1.56)	55	1.21 (0.75-1.97)	236	1.16 (0.89-1.52)	0.96 (0.58-1.59)							
	TT	220	30	0.81 (0.49-1.33)	177	1.10 (0.84-1.46)	1.36 (0.82-2.25)	21	1.01 (0.55-1.84)	114	1.15 (0.83-1.57)	1.14 (0.61-2.13)							
CYP24A1 (rs2762939)	CT+TT	691	116	0.99 (0.68-1.43)	553	1.12 (0.90-1.39)	1.13 (0.77-1.65)	76	1.15 (0.72-1.82)	350	1.16 (0.90-1.49)	1.01 (0.62-1.63)							
	TT	560	95	1.0	419	1.0	1.0	55	1.0	265	1.0	1.0							
	TC	353	56	0.90 (0.62-1.30)	292	1.10 (0.90-1.36)	1.23 (0.85-1.79)	42	1.15 (0.74-1.77)	185	1.13 (0.88-1.43)	0.98 (0.62-1.55)							
CYP24A1 (rs2181874)	CC	57	7	0.78 (0.34-1.77)	52	1.16 (0.76-1.76)	1.49 (0.65-3.42)	6	0.80 (0.30-2.15)	31	1.11 (0.68-1.80)	1.38 (0.50-3.80)							
	TC+CC	410	63	0.88 (0.62-1.25)	344	1.11 (0.91-1.36)	1.26 (0.88-1.81)	48	1.10 (0.72-1.67)	216	1.12 (0.89-1.41)	1.02 (0.66-1.59)							
	GG	560	94	1.0	414	1.0	1.0	59	1.0	260	1.0	1.0							
GC (rs7041)	GA	366	61	0.98 (0.68-1.40)	298	1.13 (0.92-1.39)	1.15 (0.80-1.67)	40	0.96 (0.62-1.48)	193	1.20 (0.94-1.52)	1.25 (0.79-1.97)							
	AA	66	10	0.88 (0.43-1.77)	69	1.43 (0.99-2.08)	1.64 (0.81-3.31)	10	1.36 (0.64-2.89)	38	1.30 (0.84-2.01)	0.96 (0.43-2.10)							
	GA+AA	432	71	0.96 (0.68-1.35)	367	1.18 (0.97-1.43)	1.23 (0.86-1.74)	50	1.02 (0.68-1.53)	231	1.21 (0.97-1.52)	1.19 (0.78-1.83)							
GC (rs4588)	GG	311	47	1.0	234	1.0	1.0	23	1.0	152	1.0	1.0							
	GT	474	83	1.25 (0.84-1.87)	387	1.06 (0.84-1.33)	0.84 (0.56-1.27)	62	1.68 (1.01-2.80)	243	1.01 (0.78-1.30)	0.60 (0.35-1.01)							
	TT	193	34	1.19 (0.72-1.96)	152	0.99 (0.75-1.32)	0.83 (0.50-1.38)	21	1.43 (0.76-2.67)	95	0.94 (0.67-1.30)	0.65 (0.34-1.26)							
GC (rs4588)	GT+TT	667	117	1.24 (0.84-1.81)	539	1.04 (0.84-1.28)	0.84 (0.57-1.24)	83	1.61 (0.99-2.62)	338	0.99 (0.77-1.26)	0.61 (0.37-1.02)							
	CC	514	79	1.0	377	1.0	1.0	58	1.0	237	1.0	1.0							
	CA	393	70	1.20 (0.84-1.72)	332	1.09 (0.89-1.34)	0.91 (0.63-1.31)	39	0.79 (0.51-1.23)	217	1.12 (0.88-1.42)	1.42 (0.89-2.24)							
GC (rs4588)	AA	84	15	1.12 (0.60-2.09)	67	1.04 (0.72-1.49)	0.92 (0.49-1.74)	11	1.13 (0.56-2.26)	33	0.78 (0.50-1.23)	0.70 (0.33-1.48)							
	CA+AA	477	85	1.19 (0.85-1.67)	399	1.08 (0.89-1.32)	0.91 (0.64-1.29)	50	0.85 (0.56-1.28)	250	1.06 (0.84-1.33)	1.25 (0.81-1.92)							

¹ adjusted for age, first degree family history of breast cancer, and mammogram use

² OR comparing risk of invasive vs. *in situ* disease

³ OR comparing risk of ER+ and PR+ vs. ER-/PR-

NE, Not Estimable