Published in final edited form as:

Menopause. 2013 March ; 20(3): 354–358. doi:10.1097/GME.0b013e318268ca46.

Breast cancer susceptibility associated with rs1219648 (*FGFR2*) and postmenopausal hormone therapy use in a population-based U.S. study

Shaneda Warren Andersen, MS^{1,2}, Amy Trentham-Dietz, PhD^{1,2}, Jonine D Figueroa, PhD³, Linda J Titus, PhD⁴, Qiuyin Cai, MD PhD⁵, Jirong Long, PhD⁵, John M Hampton, MS¹, Kathleen M Egan, ScD⁶, and Polly A Newcomb, PhD^{1,7}

¹University of Wisconsin Carbone Cancer Center, Madison, WI 53726, USA

²Department of Population Health Sciences, University of Wisconsin-Madison, Madison, WI 53726, USA

³Division of Cancer Epidemiology & Genetics, National Cancer Institute, Bethesda, MD 20892, USA

⁴Norris Cotton Cancer Center, Dartmouth Medical School, Lebanon, NH 03756, USA

⁵Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center; Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN 37235, USA

⁶Division of Cancer Prevention and Control, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL 33612, USA

⁷Cancer Prevention Program, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA

Abstract

Objective—Genome-wide association studies have consistently found variants in *FGFR2* to be associated with breast cancer. Recent reports suggest that postmenopausal hormone therapy use may modify the association between single nucleotide polymorphisms in *FGFR2* and breast cancer risk. We assessed the hypothesis that the association between rs1219648 (*FGFR2*) single nucleotide polymorphism and breast cancer risk is modified by postmenopausal hormone therapy use in a population-based case-control study.

Methods—We evaluated rs1219648 single nucleotide polymorphism for an association with breast cancer risk using data obtained from 869 postmenopausal breast cancer cases diagnosed between the years of 1995-2000 and 808 postmenopausal community controls who participated in a study conducted in three U.S. states. Detailed postmenopausal hormone therapy information was collected through a structured telephone interview and DNA samples were collected through the mail using an established mouthwash protocol. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression models adjusted for age and state of residence.

Corresponding author: Shaneda Warren Andersen, University of Wisconsin Carbone Cancer Center and Department of Population Health Sciences, University of Wisconsin-Madison, 610 Walnut St Rm 307, Madison, WI 53726, USA, phone: 608-265-9993, fax: 608-295-5330, snandersen@wisc.edu.

The authors have no conflicts of interest or disclosures.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Results—We observed a significant association with the rs1219648 and breast cancer risk (per-allele OR=1.22, 95% CI: 1.06-1.41; p-value=0.007), which did not vary significantly by ever use of estrogen plus progestogen therapy (interaction p-value=0.48). There was stronger evidence of an interaction between ever use of estrogen-only hormone therapy and increasing number of rs1219648 risk alleles to increase breast cancer risk (interaction p-value=0.08).

Conclusions—Our results are consistent with a risk association for *FGFR2* but provide limited support for interaction with hormone therapy use. The study raises the possibility that the *FGFR2* rs1219648 variant is more strongly associated with risk in estrogen-only hormone users, though this observation needs to be examined in larger studies.

Keywords

breast cancer; genetics; hormone therapy; gene-environment interaction; epidemiology

Introduction

Fibroblast growth factor receptor 2 (*FGFR2*) has been linked to breast cancer incidence in a variety of ways. *FGFR2* codes for a protein expressed in breast tumors¹ and most notably, single nucleotide polymorphisms (SNPs) in the gene have been associated with breast cancer risk in genome-wide association studies (GWAS)²⁻⁴. rs1219648 in intron 2 was the SNP most significantly associated with breast cancer risk in a two-staged GWAS conducted by Hunter et al.². Women homozygous for the risk allele had a 64% increased breast cancer risk in comparison to women with wild-type alleles. A haplotype block encompassing the same region of *FGFR2* has been shown to affect gene expression which may explain the link to breast cancer risk⁵.

Evidence suggests that *FGFR2* is more strongly associated with hormonally-related breast cancer⁶⁻⁸. In a study using pooled data from the Breast Cancer Association Consortium, the association between *FGFR2* and breast cancer incidence was stronger in women diagnosed with estrogen and progesterone receptor-positive breast cancers than in women with hormone receptor-negative tumors⁸. Most recently, gene-environment interactions between *FGFR2* and postmenopausal hormone therapy (HT) have been reported to increase breast cancer risk in some^{9,10} though not all investigations¹¹. Rebbeck et al. observed an odds ratio (OR) for breast cancer of 2.63 (95% confidence interval [CI]: 1.46-4.76) for estrogen plus progestogen HT use and homozygosity for the major allele, whereas estrogen plus progestogen hormone use and heterozygosity had an odds ratio of 0.49 (95% CI: 0.26-0.95)⁹. The association between breast cancer risk and rs3750817, another SNP in intron 2 which is not in linkage disequilibrium with rs1219648, was modified by the type of hormone therapy formulation. In the large prospective Women's Health Initiative (WHI), Prentice et al. found that when compared to never users that were homozygous for the minor allele, estrogen hormone therapy users had a decreased risk of disease with an OR of 0.34 (95% CI: 0.15-0.76), whereas estrogen plus progestogen therapy users had an OR of 0.69 (95% CI: 0.41-1.17)¹⁰. We examined the association between *FGFR2* rs1219648 genotype, HT use and breast cancer risk in a population-based case-control study.

Methods

Study Population

Data from a previously described population-based case-control study were used for this study^{12,13}. Eligible participants were selected from population lists of English-speaking females residing in Massachusetts (excluding metropolitan Boston), New Hampshire or Wisconsin. Cases included in the analysis were postmenopausal women age 36-75 with an

incident invasive breast cancer reported to state cancer registries between 1995 and 2000. Community controls were randomly selected in each state from population lists of licensed drivers if under age 65 and lists of Medicare beneficiaries (age 65). Controls were frequency matched to approximate the age distribution of the cases within five-year age strata. This study was conducted after approval from Institutional Review Boards at Dartmouth Medical School, Harvard University, the University of Wisconsin-Madison and the National Cancer Institute.

Risk factor information

Telephone interviews were used to obtain information on demographics, family history of cancer, reproductive exposures and use of exogenous hormones. Detailed information was acquired on hormone therapy usage patterns, type of formulation and duration of use. Participant interviews were conducted on average one year after a specified reference date. The reference date for each participant was defined as the date of cancer diagnosis for the cases and a comparable date for control participants based on their five-year age strata and interview date. Among eligible participants approximately 80% of cases and 76% of controls completed the interview.

Genotyping

Participants were asked to donate a buccal cell sample for genetic analyses. Samples were sent through the mail to a National Cancer Institute-affiliated laboratory for processing. DNA collection, isolation and storage were conducted according to previously described protocols¹². Whole genome amplification using multiple displacement amplification was performed at Vanderbilt University according to manufacturer's instructions (Qiagen, Valencia, CA) to increase the amount of genomic DNA. Genotyping was conducted at the Survey and Biospecimen Shared Resource, Vanderbilt University using the Taqman (5'-nuclease assay) genotyping assay in ABI PRISM 7900 Sequence Detection Systems (Applied Biosystems). 70% of interviewed cases and 61% of interviewed controls agreed to donate a genetic sample. To reduce the possibility of population stratification, all analyses were limited to participants self-identified as White/Caucasian in race (97.3% of postmenopausal participants).

Statistical Analyses

Our analysis included White postmenopausal participants who returned a DNA sample for a total of 869 cases and 808 controls. Participants were considered postmenopausal if they reported their menstrual cycles had stopped for at least the last six months prior to reference date. Hardy-Weinberg equilibrium was tested by comparing the observed to expected genotype frequencies in controls. Logistic regression was used to calculate ORs and 95% CIs for the association between breast cancer and *FGFR2* rs1219648 genotype as well as associations with established breast cancer risk factors. Under an additive genetic model, dummy variables were used to model heterozygote and minor allele homozygote associations for rs1219648. All statistical models included terms for age and state of residence. ORs were further adjusted for the following potential confounding variables: age at menarche, parity, age at first birth, ever smoking status, diabetes diagnosis and body mass index (kg/m²) one year prior to diagnosis. The association between rs1219648 and breast cancer risk showed little evidence of confounding by established breast cancer risk factors consequently results are displayed from age and state-adjusted models. A statistical test for trend in breast cancer risk by number of minor alleles present was calculated by including an ordinal term in the regression.

Potential interactions were evaluated by including cross-product terms combining recency, duration or ever use of HT with the number of minor rs1219648 alleles in multivariate

models. Ever use of HT use was defined as consecutive use of postmenopausal hormones of any kind for at least one month. Results of analyses where ever use was defined as three or more months were similar to the presented results. The hormone therapy variable was then dichotomized based on formulation type as users of estrogen-only medications or estrogen plus progestogen therapy users which included participants who had ever taken medications containing a progestogen component (combined estrogen plus progestogen ever-users N=484; progestogen-only ever-users N=16). Results were similar for the estrogen plus progestogen therapy group in analyses which did and did not include progestogen-only users. Participants taking other types of hormone formulations (N=38) were not included in sub-group analyses. HT duration was defined in approximate tertiles of use as <5, 5-9, 10 years. Current HT use was defined as use within the calendar year two years prior of the reference date. This variable was defined as such to permit time for hormone therapy to have an effect on breast cancer risk.

To elucidate whether risks differ by HT usage patterns, interactions between genotype and HT use were explored by calculating ORs for the association between rs1219648 and breast cancer risk stratified by HT ever use, formulation or current use. In analyses accounting for HT use, participants homozygous for the major allele (AA) and who had not used HT were treated as the reference group.

Results

Selected genetic and hormone therapy usage characteristics are presented in Table 1. Study participants who chose not to provide a DNA sample for genetic analyses tended to be younger than individuals who did provide a sample, but were similar in other established risk factors for breast cancer¹⁴. In this study breast cancer cases tended to have a later age at menopause and were more likely to have a family history of the disease than controls. Estrogen plus progestogen therapy users had an increased risk of breast cancer compared to never users of HT (OR=1.31, 95%CI: 1.03-1.66). Current and long-term (10 years) hormone users of any formulation had an increased risk of breast cancer. There was no significant departure from Hardy-Weinberg Equilibrium in allelic frequencies for rs1219648 among the controls (p-value=0.27). Women with one or more copies of the minor allele for rs1219648 had an increased risk of breast cancer when compared to women with both wild-type alleles (AA) with a per-allele increase risk of 22% (95%CI: 6%-41%).

We observed ever-users of HT with at least one copy of the G allele of rs1219648 had an increased risk of breast cancer when compared to never users homozygous for the major allele (Table 2). Ever-users with AG genotype had an OR of 1.38 (95%CI: 1.01-1.90) and ever-users with GG genotype had an elevated OR of 1.68 (95%CI: 1.08-2.62). Although not statistically significant the point estimates for never users with one or more copies of the minor allele were in the same direction as ever-users (AG genotype OR=1.28, 95%CI: 0.92-1.78; GG genotype OR=1.26, 95%CI: 0.81-1.98). The observed risk associated with rs1219648 minor allele genotype did not differ significantly by type of HT used although excess risk among minor allele homozygotes was more prominent in estrogen therapy users (OR=1.93, 95%CI: 1.11-3.36) than those that used estrogen plus progestogen therapy (OR=1.25, 95%CI: 0.69-2.25). Moreover, there was evidence of an interaction among ever users of estrogen-only hormone therapy and the risk allele of rs1219648 to increase breast cancer risk (interaction p-value=0.08) but the interaction between rs1219648 minor alleles and estrogen plus progestogen therapy was not evident (interaction p-value=0.48).

Current users with at least one copy of the risk allele had an increased breast cancer risk when compared to never users with AA genotype (Table 2). Current ever-users with GG genotype had a 69% increased risk of breast cancer compared to wildtype never users. There

was suggestive, but not statistically significant, evidence for interaction between current estrogen HT and increasing number of rs1219648 minor alleles (p-value=0.10). Current estrogen plus progestogen therapy use did not modify the association between the *FGFR2* variant and breast cancer risk (p-value=0.60). Overall, estrogen plus progestogen therapy users had an elevated risk of breast cancer in comparison to never users with AA genotype. Tests for interaction between duration of HT and genotype were null (p-value=0.55) irrespective of formulation type.

Discussion

Consistent with previous reports focused on this region of *FGFR2*^{2-4, 6, 15, 16}, we found an increased risk of breast cancer with increasing number of risk alleles of *FGFR2* rs1219648. We also assessed whether the relationship between rs1219648 and invasive breast cancer risk was modified by HT use in a population-based sample as previous studies have reported a difference in the effect SNPs in *FGFR2* exhibit on breast cancer risk according to hormone therapy use^{9, 10}. Variants in *FGFR2* are hypothesized to act through hormonal pathways to influence breast cancer risk because of the variants' stronger association with hormone receptor-positive tumors⁸.

In a study involving 1225 participants, Rebbeck et al.⁹ reported a significant interaction between the use of estrogen plus progestogen therapy and rs1219648 on breast cancer risk (p-value=0.01). Estrogen plus progestogen therapy users who were wildtype at this locus were at an increased risk of disease compared to never users with the same genotype (OR=2.63; 95%CI: 1.46-4.76). Our study found a weaker effect with an OR of 1.31 (95%CI: 0.87-1.97). Rebbeck et al. did not assess whether estrogen-only formulations modified the association between *FGFR2* and breast cancer risk. In a separate study, the Women's Health Initiative did not find evidence of interaction between the type of HT formulation used and rs1219648 genotype. The WHI observed no difference in breast cancer risk associated with the minor allele of rs1219648 in either the estrogen therapy arm (p-value=0.42) or the estrogen plus progestin therapy arm (p-value=0.66) of the randomized trial¹⁰.

We observed suggestive, but not statistically significant, evidence of an interaction with current estrogen therapy use but did not detect an interaction between *FGFR2* and current estrogen plus progestogen therapy use. Recently, the Million Women Study explored interactions between current hormone therapy use and rs2981582, a SNP located in *FGFR2* in strong linkage disequilibrium with rs1219648. The investigators found no evidence of difference in the increased breast cancer risk associated with the minor allele of rs2981582 by current HT use or hormone therapy formulation¹¹. Analysis restricted to cases diagnosed with estrogen-receptor positive disease also did not support an interaction between *FGFR2* and current HT use. Our study and the Million Women Study both found little evidence of an interaction between current HT use and *FGFR2* SNPs; additionally we also evaluated whether the duration of hormone therapy use modified the effect of *FGFR2* genotype on breast cancer risk and found no evidence of heterogeneity in risk by the duration of HT use.

The strength of the current study was the comprehensive interview data on HT usage patterns, duration and type of formulation utilized to evaluate interactions. We believe recall bias is unlikely to play a role in our findings as the genotype assessment is not subject to this type of error. However, breast cancer cases may suspect that their diagnosis was related to previous hormone therapy use and be more thoughtful about their usage patterns than controls answering the same question which could lead to recall bias. However, we assert that the categorization of hormone therapy use into never versus ever use is reliably answered and less susceptible to bias than more specific HT questions. Hormone therapy formulation may be a harder to recall; this error would most likely be non-differential

potentially diluting the association towards the null. A limitation of the study, however, was our lack of information on hormone-receptor status. Most ^{1, 6, 8, 17}, though not all ¹¹ studies have suggested stronger associations between *FGFR2* and estrogen receptor-positive tumors. Although the majority of diagnosed breast cancers are estrogen receptor-positive ¹⁸ our findings may be attenuated towards the null by including estrogen receptor-negative tumors in the analyses. Our results are expected to be generalizable to similar populations of postmenopausal women throughout the United States. The association between rs1219648 and breast cancer risk is not likely to vary if the SNP is present in the population. We found evidence that estrogen-only hormone therapy may modify this association, yet, replication of this finding in larger studies is needed.

Conclusions

In summary, these data suggest that the association of rs1219648 with breast cancer risk does not appear to be strongly influenced by hormone therapy use or duration of hormone therapy. The study raises the possibility that the *FGFR2* rs1219648 variant is more strongly associated with risk in estrogen therapy users though this observation needs to be examined in larger studies.

Acknowledgments

This work was supported by grants from the National Institutes of Health Cancer Institute [grant numbers CA47147, CA47305, CA69664, CA82004] the Avon Foundation and by Intramural Research Funds of the National Cancer Institute, Department of Health and Human Services, USA. Genotyping assays were supported by the National Institutes of Health [grant number R01CA124558]. The genotyping assays were performed at the Vanderbilt University Survey and Biospecimen Share Resource, which is supported in part by the Vanderbilt-Ingram Cancer Center [grant number P30 CA68485]. The authors would like to thank all the study participants and staff for their individual contributions and time.

Funding: This work was supported by grants from the National Institutes of Health Cancer Institute [grant numbers CA47147, CA47305, CA69664, CA82004] the Avon Foundation and by Intramural Research Funds of the National Cancer Institute, Department of Health and Human Services, USA. Genotyping assays were supported by the National Institutes of Health [grant number R01CA124558]. The genotyping assays were performed at the Vanderbilt University Survey and Biospecimen Share Resource, which is supported in part by the Vanderbilt-Ingram Cancer Center [grant number P30 CA68485].

References

1. Luqmani YA, Graham M, Coombes RC. Expression of basic fibroblast growth factor, FGFR1 and FGFR2 in normal and malignant human breast, and comparison with other normal tissues. *Br J Cancer*. 1992; 66(2):273–80. [PubMed: 1380281]
2. Hunter DJ, Kraft P, Jacobs KB, et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. *Nat Genet*. 2007; 39(7):870–4. [PubMed: 17529973]
3. Easton DF, Pooley KA, Dunning AM, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. *Nature*. 2007; 447(7148):1087–93. [PubMed: 17529967]
4. Gold B, Kirchhoff T, Stefanov S, et al. Genome-wide association study provides evidence for a breast cancer risk locus at 6q22.33. *Proc Natl Acad Sci U S A*. 2008; 105(11):4340–5. [PubMed: 18326623]
5. Meyer KB, Maia AT, O'Reilly M, et al. Allele-specific up-regulation of FGFR2 increases susceptibility to breast cancer. *PLoS Biol*. 2008; 6(5):e108. [PubMed: 18462018]
6. Liang J, Chen P, Hu Z, et al. Genetic variants in fibroblast growth factor receptor 2 (FGFR2) contribute to susceptibility of breast cancer in Chinese women. *Carcinogenesis*. 2008; 29(12):2341–6. [PubMed: 18845558]
7. Garcia-Closas M, Chanock S. Genetic susceptibility loci for breast cancer by estrogen receptor status. *Clin Cancer Res*. 2008; 14(24):8000–9. [PubMed: 19088016]

8. Garcia-Closas M, Hall P, Nevanlinna H, et al. Heterogeneity of breast cancer associations with five susceptibility loci by clinical and pathological characteristics. *PLoS Genet.* 2008; 4(4):e1000054. [PubMed: 18437204]
9. Rebbeck TR, DeMichele A, Tran TV, et al. Hormone-dependent effects of FGFR2 and MAP3K1 in breast cancer susceptibility in a population-based sample of post-menopausal African-American and European-American women. *Carcinogenesis.* 2009; 30(2):269–74. [PubMed: 19028704]
10. Prentice RL, Huang Y, Hinds DA, et al. Variation in the FGFR2 gene and the effects of postmenopausal hormone therapy on invasive breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2009; 18(11):3079–85. [PubMed: 19861516]
11. Travis RC, Reeves GK, Green J, et al. Gene-environment interactions in 7610 women with breast cancer: prospective evidence from the Million Women Study. *Lancet.* 375(9732):2143–51. [PubMed: 20605201]
12. Garcia-Closas M, Egan KM, Abruzzo J, et al. Collection of genomic DNA from adults in epidemiological studies by buccal cytobrush and mouthwash. *Cancer Epidemiol Biomarkers Prev.* 2001; 10(6):687–96. [PubMed: 11401920]
13. Garcia-Closas M, Egan KM, Newcomb PA, et al. Polymorphisms in DNA double-strand break repair genes and risk of breast cancer: two population-based studies in USA and Poland, and meta-analyses. *Hum Genet.* 2006; 119(4):376–88. [PubMed: 16485136]
14. Sprague BL, Trentham-Dietz A, Garcia-Closas M, et al. Genetic variation in TP53 and risk of breast cancer in a population-based case control study. *Carcinogenesis.* 2007; 28(8):1680–6. [PubMed: 17449902]
15. Udler MS, Meyer KB, Pooley KA, et al. FGFR2 variants and breast cancer risk: fine-scale mapping using African American studies and analysis of chromatin conformation. *Hum Mol Genet.* 2009; 18(9):1692–703. [PubMed: 19223389]
16. Raskin L, Pinchev M, Arad C, et al. FGFR2 is a breast cancer susceptibility gene in Jewish and Arab Israeli populations. *Cancer Epidemiol Biomarkers Prev.* 2008; 17(5):1060–5. [PubMed: 18483326]
17. Stacey SN, Manolescu A, Sulem P, et al. Common variants on chromosome 5p12 confer susceptibility to estrogen receptor-positive breast cancer. *Nat Genet.* 2008; 40(6):703–6. [PubMed: 18438407]
18. Anderson WF, Chatterjee N, Ershler WB, Brawley OW. Estrogen receptor breast cancer phenotypes in the Surveillance, Epidemiology, and End Results database. *Breast Cancer Res Treat.* 2002; 76(1):27–36. [PubMed: 12408373]

Table I

Selected participant characteristics by breast cancer status.

Characteristic	Controls (N=808)	Cases (N=869)	Odds Ratio (95% Confidence Interval)
Age at interview (mean)	60.5	60.5	
Family History (% , yes)	15.5	23.3	1.64 (1.28-2.11)
Age at menopause			
<45	142	128	0.86 (0.63-1.18)
45-49	190	191	0.93 (0.71-1.22)
50-54	244	263	1 (ref.)
55	57	94	1.54 (1.06-2.24)
Hormone therapy use			
Never	359	352	1 (ref.)
Ever	446	515	1.13 (0.92-1.37)
Current	369	468	1.26 (1.02-1.55)
Formulation			
Estrogen	215	208	0.93 (0.73-1.19)
Estrogen+progestogen	216	284	1.31 (1.03-1.66)
Duration (years)			
>5	171	146	0.83 (0.63-1.09)
5-9	130	148	1.13 (0.84-1.50)
10	145	221	1.47 (1.14-1.91)
rs1219648			
AA	294	263	1 (ref.)
AG	403	464	1.29 (1.04-1.59)
GG	111	142	1.45 (1.08-1.97)
Per-allele			1.22 (1.06-1.41)

Table II

The association between ever or current postmenopausal hormone therapy use and breast cancer risk by FGFR2 rs1219648 genotype.

Genotype	Never use			Ever use			Estrogen use			Estrogen+progestogen use		
	Controls (N)	Cases (N)	Odds ratio (95% CI) ^a	Controls (N)	Cases (N)	Odds ratio (95% CI) ^a	Controls (N)	Cases (N)	Odds ratio (95% CI) ^a	Controls (N)	Cases (N)	Odds ratio (95% CI) ^a
AA	132	110	1 (ref)	161	153	1.05 (0.74-1.49)	79	53	0.73 (0.47-1.14)	77	94	1.31 (0.87-1.97)
AG	171	184	1.28 (0.92-1.78)	230	280	1.38 (1.01-1.90)	110	111	1.10 (0.76-1.61)	110	156	1.71 (1.18-2.48)
GG	56	58	1.26 (0.81-1.98)	55	82	1.68 (1.08-2.62)	26	44	1.93 (1.11-3.36)	29	34	1.25 (0.69-2.25)
p-interaction						0.55			0.08			0.48
Genotype	Never use			Current use ^b			Estrogen current use ^b			Estrogen+progestogen current use ^b		
	Controls (N)	Cases (N)	Odds ratio (95% CI) ^a	Controls (N)	Cases (N)	Odds ratio (95% CI) ^a	Controls (N)	Cases (N)	Odds ratio (95% CI) ^a	Controls (N)	Cases (N)	Odds ratio (95% CI) ^a
AA	132	110	1 (ref)	137	141	1.16 (0.81-1.66)	72	60	0.93 (0.60-1.46)	66	87	1.43 (0.94-2.20)
AG	171	184	1.28 (0.92-1.78)	184	255	1.63 (1.17-2.26)	93	114	1.35 (0.92-2.00)	91	146	1.95 (1.33-2.86)
GG	56	58	1.26 (0.81-1.98)	48	72	1.69 (1.06-2.68)	27	40	1.65 (0.94-2.90)	24	32	1.45 (0.78-2.69)
p-interaction						0.64			0.10			0.60

^aOdds ratios adjusted for age and state of residence.

^bCurrent use category includes participants that reported using hormone therapy within the calendar year two years prior of the reference date. Abbreviation: CI, confidence interval; ref, reference category.