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The effect of genetic variants on the relationship between statins and breast cancer in postmenopausal women in the Women's Health Initiative observational study

Cathryn H. Bock[1], **Allison M. Jay**[2], **Gregory Dyson**[1], **Jennifer L. Beebe-Dimmer**[1], **Michele L. Cote**[1], **Lifang Hou**[3], **Barbara V. Howard**[4], **Pinkal Desai**[5], **Kristen Purrington**[1], **Ross Prentice**[6], and **Michael S. Simon**[1]

[1]Karmanos Cancer Institute, Wayne State University School of Medicine, 4100 John R, Detroit, MI 48201, USA

[2]St. John Health System, Van Elslander Cancer Center, 19229 Mack Ave, Grosse Pointe Woods, MI 48236, USA

[3]Department of Preventive Medicine and Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, 675 North St. Clair, Chicago, IL 60611, USA

[4]Medstar Health Research Institute and Georgetown/Howard Universities Center for Clinical and Translational Science, 6525 Belcrest Road, Suite 700, Hyattsville, MD 20782, USA

[5]Division of Hematology/Oncology, Weill Cornell Medical College, 1300 York Ave, New York, NY 10065, USA

[6]Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N, PO Box 19024, Seattle, WA 98109, USA

Abstract

Purpose—Statins have been postulated to have chemopreventive activity against breast cancer. We evaluated whether germline genetic polymorphisms modified the relationship between statins and breast cancer risk using data from the Women's Health Initiative. We evaluated these interactions using both candidate gene and agnostic genome-wide approaches.

Methods—To identify candidate gene–statin interactions, we tested interactions between 22 SNPS in nine candidate genes implicated in the effect of statins on lipid metabolism in 1687 cases and 1687 controls. We then evaluated statin use interaction with the remaining 30,380 SNPs available in this sample from the CGEMS GWAS study.

Results—After adjusting for multiple comparisons, no SNP interactions with statin usage and risk of breast cancer were statistically significant in either the candidate genes or genome-wide approaches.

Compliance with ethical standards

Conflicts of interest None of the authors has a conflict of interest.

Conclusions—We found no evidence of SNP interactions with statin usage for breast cancer risk in a population of 3374 individuals. These results suggest that genome-wide common genetic variants do not moderate the association between statin usage and breast cancer in the population of women in the Women's Health Initiative.

Keywords

GWAS; Breast cancer; SNPS; Cholesterol; Statins

Introduction

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are the most widely prescribed cholesterol-lowering drugs used in the United States, with an estimated 11.7% of US adults taking statins for cholesterol reduction in 2003–2004, and a trend of increasing use [1]. Statins are a logical candidate for cancer chemoprevention, as they have multiple cellular effects beyond lowering cholesterol, including inhibition of rho GTPases [2, 3], induction of apoptosis [4], and anti-inflammatory effects [5].

There is significant variation in inter-individual response to statins, and genetic differences may play a role in this variation. Inherited variation may have important implications in terms of precision medicine. Genetic variants have been implicated in the efficacy of statin therapy on lowering serum cholesterol [6], as well as clinical outcomes after myocardial infarction [7], and the risk of developing statin-induced myopathy [8]. Evidence for a relationship between statin use and breast cancer risk is mixed in published literature. Statins have been shown to inhibit breast cancer cell proliferation in studies of breast cancer cell lines [9] and some rodent models [10], and statins have also been shown to be carcinogenic in other rodent models [11]. Epidemiologic studies have yielded mixed results as well, with several reporting no relationship between statins and breast cancer incidence [12–21] and others describing either an increased risk of breast cancer [22–27] or a reduction in breast cancer risk [13, 28–32]. Two meta-analyses, one of 7 randomized controlled trials and nine observational studies [33] and the other of 14 randomized controlled trials [34] yielded no significant associations between statins and breast cancer risk.

There are a number of candidate genes related to statin therapy response associated with the modulation of LDL or HDL cholesterol levels [35, 36] and risk for cardiovascular disease that are also likely to modify the effect of statins on cancer incidence. Medina examined the role of alternative splicing of exon 13 of *HMGCR* as a marker of statin efficacy and as a chemopreventive agent for colorectal cancer (CRC) [37], and Lipkin et al. [38] described a SNP in the *HMGCR* gene (rs12654264) that significantly modified the protective association between statins and CRC risk.

In this study, we assessed whether inherited genetic polymorphisms modified the relationship between statins and breast cancer risk using data from the Women's Health Initiative (WHI). We evaluated these interactions using both candidate gene and agnostic genome-wide approaches.

Methods

Study population

The study population was derived from a case–control study nested within the much larger WHI observational study (OS). Details of the WHI study have been described extensively in previous publications [39–41]. In brief 93,676 postmenopausal women aged 50–79 were enrolled in an OS cohort in 40 US clinical centers from January 1, 1994 through December 31, 1998. Follow-up continued from study initiation until planned termination on March, 2005, and thereafter for participants providing re-consent with data collection updated through September, 2010 for an average of 10.8 (SD 3.3) years of follow-up. For the purposes of this analysis, women in the WHI OS who were included in the cancer genetics markers of susceptibility (CGEMS) genome-wide association study (GWAS) of breast cancer [42] were eligible. A nested case–control approach was used for the CGEMS study, and served as the source population for the study presented here. Breast cancer cases and controls of European descent were matched 1:1 on age at screening, enrollment date, hysterectomy status at baseline, and history of breast cancer at study entry. Of the 2395 cases and 2410 controls included in the CGEMS GWAS, there were 1687 matched case–control pairs with genotype information available for both cases and controls and no missing data for any of the significant potential confounding variables (described below). These 1687 matched pairs were included in the analyses presented here.

Genotype data

Genotype data were available for the 30,380 SNPs genotyped for the CGEMS GWAS as part of the stage 2 replication set in the WHI cases and controls. SNP selection criteria details, genotyping methods, and quality control measures have been described previously [42]. We identified 12 candidate genes based on a review of published studies of genetic loci implicated in the effect of statins on lipid metabolism: *PCSK9, KIF6, LDLR, HMGCR, APOB, LPL, APOE 7, SMARCA4, CETP, APOA1, ABCB1,* and *CYP7A1* [7, 35, 36, 38, 43]. A search of the CGEMS genotyped markers for SNPs within each of the candidate genes and the regions 60 kb upstream or downstream from the gene ends was conducted using the UCSC genome browser. This process identified a total of 22 candidate SNPs in across 9 of the 12 candidate genes. The three genes not represented are *APOA1*, *CYP7A1*, and *LDLR*. The remaining genotyped SNPs were included in the agnostic analyses, described below.

The dominant genotype model was used for all analyses, with homozygotes for the major allele of each SNP serving as the reference genotype, and the heterozygotes and homozygotes for the minor allele combined to form the comparison group.

Statin exposure

Women’s Health Initiative observational study participants were asked to bring all current prescription medications to their first screening interview, and clinic interviewers entered each medication name directly from the containers into the WHI database, which assigned drug codes using Medispan software (First DataBank, Inc., San Bruno, CA). At the time of the visit, women also reported duration of use for each current medication. Statin use was

defined as use of any 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor reported at the baseline.

Statistical analysis

Associations between the following baseline measures and breast cancer risk were evaluated using the Chi-square test: age (10 year categories), education (none or some high school, high school or GED, some college or more), smoking (never, past, current), alcohol use (none, < 1 drink/week, between 1 and 7 drinks/week, ≥ 7 drinks/week), physical activity (none, between 0 and 3.75 MET/week, between 3.75 and 8.75 MET/week, between 8.75 and 17.5 MET per week, ≥ 17.5 MET/week), percent energy from fat (< 30, ≥ 30%), BMI (< 25, 25–30, > 30), waist circumference (≤ 88, > 88 cm), had a care provider, history (none, < 1 drink/week, between 1 and 7 drinks/week, > 7 drinks/week), physical activity (none, between 0 and 3.75 MET/week, between 3.75 and 8.75 MET/week, between 8.75 and 17.5 MET per week, > 17.5 MET/week), percent energy from fat (< 30, > 30%), BMI (< 25, 25–30, > 30), waist circumference (< 88, > 88 cm), had a care provider, history of angina, history of high cholesterol, history of CVD, mammogram in the last 2 years, family history of breast cancer, age of menarche (< 11, between 12 and 13, 14 years old), ever had a full-term birth, age at first birth (no full term, < 20 between 20 and 30, > 30), number of live births (none, between 1 and 2, > 3), of angina, history of high cholesterol, history of CVD, mammogram in the last 2 years, family history of breast cancer, age of menarche (< 11, between 12 and 13, ≥ 14 years old), ever had a full-term birth, age at first birth (no full term, < 20 between 20 and 30, ≥ 30), number of live births (none, between 1 and 2, ≥ 3), history of breast disease (no; yes, 1 biopsy; yes, 2 biopsies), hysterectomy, bilateral oophorectomy, unopposed estrogen use (never, past, current < 5, current 5–10, current > 10 years), estrogen plus progesterone use (never, past, current < 5, current 5–10, current > 10 years), general health (fair/poor, good, very good, excellent), history of diabetes, Gail risk score (≤ 1.67, > 1.67), statin use, and statin type used (none, hydrophilic, lipophilic). These variables were then used to create a model of breast cancer risk using conditional logistic regression for the matched case–control pairs.

Variables that were univariably statistically significant at a relaxed p value of 0.20 were combined into a multivariable model. Backwards stepwise selection using the Akaike information criterion (AIC) was then applied to this multivariable model to select a parsimonious conditional logistic regression model. Individuals and their matched cases/control that were missing any of the resultant statistically significant variables were eliminated from the model-building dataset. Pairwise interactions of variables in the parsimonious model were examined for statistical significance. Next, the baseline statin use status (yes or no) variable and it's interactions with the variables from this factor model were then examined for statistical significance. The AIC was again used to eliminate non-statistically significant statin interaction terms. Finally, collapsing of adjacent levels of variables was examined. The resulting model was then considered our baseline traditional risk factor (TRF) model.

Two separate SNP analysis approaches were undertaken. The first used a candidate gene approach, and examined 22 SNPs in or near nine candidate lipid metabolism genes for

interactions with baseline statin status; while the second implemented an agnostic approach across the genome, and investigated the remaining 30,358 SNPs for interactions with baseline statin status. For both approaches, the marginal effect of each SNP (univariably) was added to the TRF model and tested against a model adding the marginal effect of each SNP and the interaction effect of the SNP with statin status. A Bonferroni adjustment was employed to determine statistical significance for the candidate gene analysis, as it is driven by a lipid-gene hypothesis (critical p value = 0.05/22 = 0.0023). We computed the false discovery rate (FDR) to evaluate the significance of the remaining 30,358 SNPs.

Results

Our case–control study population included 1687 invasive breast cancer cases and 1687 matched controls (Table 1). Cases were more likely to have a Gail risk score greater than 1.67, with 57% of cases with a high score compared with 48% of controls. Other highly significant differences (p value < 0.001) between the case and control groups included cases having a greater likelihood of a family history of breast cancer (20% vs. 15%, respectively), a history of one or more prior breast biopsies (33% vs. 22%), and current (at WHI enrollment) estrogen and progesterone (E+P) use (31% vs. 23%) than controls. The prevalence of statin use at baseline was similar between cases and controls (7% and 8%, respectively, p value = 0.15). The traditional risk factor model (excluding statin use status) included the following variables: high Gail risk score indicator (> 1.67), E+P use status ("never," "past/current less than 5 years," and "current greater than 5 years"), waist circumference indicator (> 88 cm), benign breast disease status, and percentage of energy from fat (> 30%). There were no significant interactions among these variables predicting disease status.

When we evaluated the statin variable in the model, an interaction between statin use and categorized waist circumference, and an interaction between statin status and E+P use were subsequently statistically significant; the final traditional risk factor model is detailed in Table 2. It should be noted that care must be taken when interpreting a statin effect, since statin use (yes vs. no) interacts with multiple other predictor variables in the model. From Table 1, we see that marginally, statins are not associated with breast cancer risk. The effect of statin use on breast cancer risk is only observed through statistical interactions with other risk factors. Statin use has a protective effect for women with a waist circumference < 88 cm (OR 0.57, 95% CI 0.36, 0.90), for women on no E+P treatment (OR 0.66, 95% CI 0.46, 0.95), and for women with past use of less than 5 years E+P treatment (OR 0.11, 95% CI 0.01, 0.94). Each SNP was added marginally and in an interaction term with statin use to the traditional risk model detailed in Table 2. Figure 1 shows the Manhattan plot for all 30,380 SNPs measured in the database, including vertical lines indicating the nominal 0.05 significance level and the minimum p value (1.647×10^{-6}) required to achieve an FDR of at most 0.05.

Of the 22 SNPs in candidate statin pathway genes, two were nominally significant: rs1529711 in the *CARM1* gene [near candidate gene *SMARC4,* minor allele frequency (MAF) 15%], p_{int} = 0.04, and rs9282564 in the ABCB1 gene (MAF 10%), p_{int} = 0.01 (Table 3). None of the candidate pathway gene SNPs were statistically significant after Bonferroni

correction. When the remaining 30,358 GWAS SNPs were examined for interactions with statin use, no SNPs achieved statistical significance using a 5% false discovery rate (Fig. 1). The GWAS SNP with the greatest evidence for interaction with statin use on breast cancer risk was rs2875218 in *PRDX3P3* (p_{int} = 0.0000076, data not shown), a pseudogene on chromosome 13.

Discussion

We used epidemiologic and genotype data from WHI subjects included in the NCI Cancer CGEMS GWAS in breast cancer to determine whether there was an interaction between inherited polymorphisms within statin-related genes and statin use in association with breast cancer risk. Our results suggested that two SNPs (rs1529711 and rs9282564) near candidate genes (*SMARC4* and *ABCB1*, respectively) were effect modifiers of statins on breast cancer risk. Genetic associations such as these, if confirmed, may have implications in terms of personalized medicine, given that statin efficacy in relation to breast cancer risk may be increased or decreased in individuals dependent on inherited genetic polymorphisms. An agnostic analysis of interactions between statin use and 30,358 SNPs from across the genome did not identify any SNPs that met the FDR level of statistical significance. There is significant variation in inter-individual response to statins, and genetic differences may play a role in this variation. Differential response to statins has also been reported for a variant of the *KIF6* gene. Individuals with variant rs20455 were found to have significantly greater benefit from intensive statin therapy versus non-carriers [7]. Furthermore, certain genotypes may contribute to a greater risk of adverse events with statin therapy. This was illustrated in a GWAS study of 85 cases with statin-induced myopathy compared to 90 controls all of whom were taking 80 mg of simvastatin daily which showed a strong relationship between genotype and myopathy. The investigators reported that individuals who had the rs4363657 SNP within the *SLCO1B1* gene on chromosome 12 were more likely to develop statin-induced myopathy [8]. The *SLCO1B1* gene encodes an organic anion-transporting polypeptide which has been found to be important in the regulation of hepatic uptake of statins. A second variant, rs4149056, was also found to be associated with both myopathy and the cholesterol-lowering effects of simvastatin.

Proposed mechanisms for the effect of statins on breast cancer cell proliferation have been mixed [9–11]. One hypothesized mechanism by which statins inhibit tumor growth is the downregulation of metalloproteinases (MMPs). MMPs are involved in the degradation of extracellular matrix components, and are involved in tumor growth, invasion, and metastasis. It has been hypothesized that lipophilic statins (such as simvastatin and lovastatin) may reduce *MMP2* and *MMP9* gene transcription and inhibit peripheral mononuclear cell proliferation by decreasing the release of inactive MMP preforms [44].

There is a growing body of literature suggesting a differential effect of statins on cancer prevention based on the type or class of statin [2, 45]. Statins are classified based on their solubility in octanol (lipophilicity) or water (hydrophilicity) [46, 47], and lipophilic statins (lovastatin, simvastatin, fluvastatin) penetrate the plasma membrane while hydrophilic statins (pravastatin and atorvastatin) do not [2]. It is postulated that the cellular uptake of lipophilic statins may be associated with their inhibition of cell growth [2, 45] and this

concept is supported by a cell culture study in which only lipophilic statins were shown to have anti-cancer activity [48]. It has also been hypothesized that pravastatin, which is hydrophilic, may promote the development of cancer by causing an induction of mevalonate synthesis in extra-hepatic tissue [2]. Of the clinical studies evaluating statins and breast cancer, relatively few have looked at specific statin preparations or class [13, 21, 22, 28, 30, 31, 49]. The results from these studies have been mixed, with either no relationship noted [21], a suggestion of an increased risk of breast cancer [23, 24, 49], or a reduction in risk [13, 30–32]. In one study, only fluvastatin (lipophilic) was associated with a lower risk of breast cancer (OR 0.5, 95% CI 0.3–0.8) [32], and in another, the specific type of statin was not associated with breast cancer risk, although use of statins for more than 5 years was related to a slight decrease in risk (OR 0.7, 95% CI 0.4–1.0) [13]. In a record-linkage cohort study from Finland, a marginal reduction in breast cancer risk was noted for users of simvastatin (lipophilic statin) [hazards ratio (HR) 0.97, 95% CI 0.95–0.99] [30] and in the Heart Protection Study slightly fewer breast cancers were found among women randomly assigned to simvastatin compared with placebo [31].

To examine the association between statin use and breast cancer, Cauley and colleagues used data from the Women's Health Initiative (WHI) [28], which consisted of 4383 incident cases of invasive breast cancer over an average of 6.7 years of follow-up. The results showed no significant association for users versus non-users of statins overall or any trend by duration of use although the investigators demonstrated an 18% reduction in breast cancer risk (HR 0.82, 95% CI 0.7–0.97, $p = 0.02$) among users of lipophilic statins (simvastatin, lovastatin, and fluvastatin). In addition, women who used estrogen and statins had a reduction in breast cancer risk that was of borderline statistical significance. However a recent update of the WHI data showed only a marginal, non-significant reduction in breast cancer risk for simvastatin alone (HR 0.878, 95% CI 0.71–1.07) [50].

There are a number of candidate genes related to statin therapy response. Poduri et al. [36], examined 18 SNPs in six genes: *HMGCR, CETP, APOA1, ABCB1, CYP3A4, and CYP7A1*. Variant alleles of *ABCB1* (-41A/G), *HMGCR* SNP 29 G/T, rs5908 A/G, rs12916 C/T, and *CYP7A1*-204 A/C were significantly associated with decreased LDL cholesterol levels. Kathiresen et al. [35] studied 11 SNPs in nine genes including: *APOB, PCSK9, LDLR, CEETP, LIPC, LPL, APOE, HMGCR, and LDLR*. Her results showed that a genotype score of nine (based on the number of unfavorable alleles) was associated with modulation of LDL or HDL cholesterol levels, and was an independent risk factor for incident cardiovascular disease. Medina et al. looked at studies examining the role of alternative splicing of exon 13 of *HMGCR*, finding it a marker of statin efficacy as well as a chemopreventive agent for colorectal cancer (CRC) [37]. Lipkin et al. [38] described a SNP in the *HMGCR* gene (rs12654264) that significantly modified the protective association between statins and CRC risk. Compared with non-users, the unadjusted OR of CRC among statin users with the A/A genotype of rs12654264 in *HMGCR* was 0.3 (95% CI 0.18–0.51) and among statin users with the T/T genotype was 0.66 (95% CI, 0.41–1.06; p-interaction = 0.0012). This genetic variant (A/A genotype of rs12654264) was also associated with lower serum levels of LDL among all cases and controls. *SMARC4* is a SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, and was identified as a candidate effect modifier in a genome-wide study of statin-induced myopathy [8].

Strengths of this investigation include the large sample size and prospective design of the WHI study. Since cases and controls had no history of cancer at baseline, their statin use would not be biased. Also, all reported cancer diagnoses during follow-up were centrally adjudicated using medical records by the WHI. Because only baseline statin use was examined, we know that exposure was underestimated in both cases and controls; this would likely bias results toward the null. Also, we had inadequate numbers to stratify statin exposure on lipophilic status. Our analyses were also limited by the genotyping panel available from CGEMS, which was not a full GWAS, but rather a secondary panel to follow-up on top hits from the initial GWAS.

In conclusion, we did not observe an independent association between statins and breast cancer incidence in this nested matched case–control study, and this is in agreement with the larger prospective WHI study by Desai [50]. SNPs in/near two genes associated with statin efficacy, *SMARC4* and *ABCB1,* were suggested to modify the effect of statins on breast cancer risk; however, the interaction odds ratios did not achieve Bonferroni-corrected statistical significance. An examination of SNPs across the genome did not identify any SNPs that interacted significantly with baseline statin use in breast cancer risk. This suggests that the genetic profiles of individuals likely do not greatly influence the efficacy of statins in reducing breast cancer risk, and thus will not be useful in identifying women for whom statins provide significant risk reduction.

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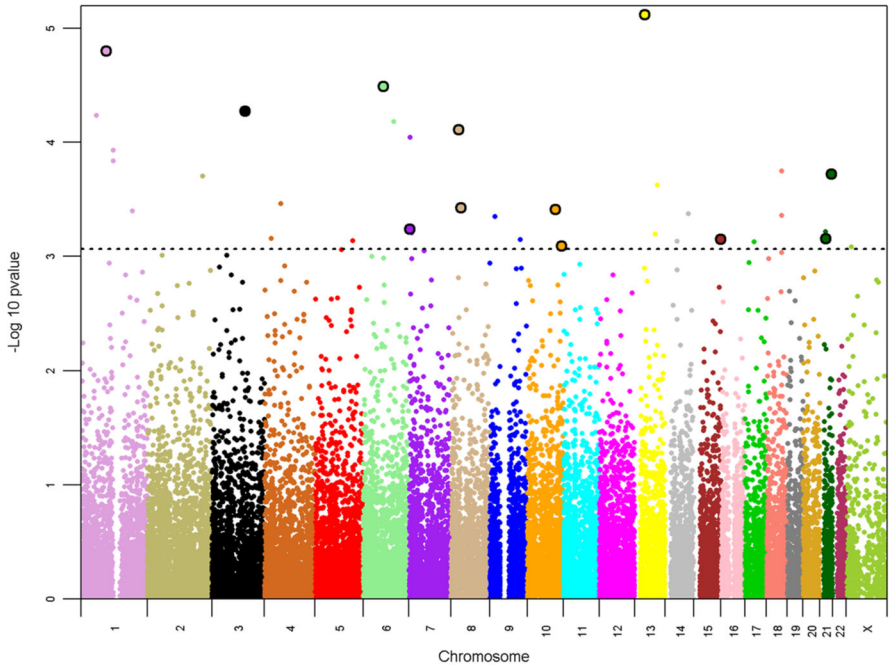

Fig. 1.

Manhattan plot of the *p* value for the interaction effect of each of the 30,380 SNPs with statin status after adjusting for traditional risk factors. Horizontal lines indicate the nominal 0.05 significance level and the necessary significance threshold to achieve an FDR of 0.05, given that we tested 30,380 SNPs

Table 1

Baseline characteristics of cases and controls

Characteristic	Controls *N* (%)	Cases *N* (%)	*p*-value*
Age (years)			1.00
50–59	453 (0.27)	452 (0.27)	
60–69	782 (0.46)	784 (0.46)	
70–79	452 (0.27)	451 (0.27)	
Education			0.30
None-some high school	54 (0.03)	47 (0.03)	
High school/GED	292 (0.17)	262 (0.16)	
More than high school/GED	1336 (0.79)	1366 (0.82)	
Smoking			0.16
Never	834 (0.50)	780 (0.47)	
Past	731 (0.44)	784 (0.47)	
Current	99 (0.06)	102 (0.06)	
Percent energy from fat >= 30%			0.03
No	931 (0.55)	867 (0.51)	
Yes	756 (0.45)	820 (0.49)	
BMI (kg/m^2)			0.004
Less than 25	754 (0.45)	681 (0.41)	
Between 25 and 30	577 (0.34)	573 (0.34)	
Greater than or equal to 30	344 (0.21)	419 (0.25)	
Waist circumference (cm)			0.00
Less than or equal to 88	1182 (0.70)	1100 (0.65)	
Greater than 88	505 (0.30)	587 (0.35)	
Mammogram in the last 2 years			0.11
No	199 (0.12)	169 (0.10)	
Yes	1444 (0.88)	1474 (0.90)	
Family history of breast cancer			< 0.001
No	1373 (0.85)	1281 (0.80)	
Yes	239 (0.15)	326 (0.20)	
Age at first birth (years)			0.10
Never pregnant	154 (0.09)	195 (0.12)	
No full term birth	178 (0.11)	153 (0.09)	
Less than 20	167 (0.10)	156 (0.09)	
Between 20 and 29	1029 (0.62)	1015 (0.61)	
Greater than or equal to 30	137 (0.08)	151 (0.09)	
Number of live births			0.001
None	191 (0.11)	247 (0.15)	
1 or 2	583 (0.35)	620 (0.37)	
3 or more	908 (0.54)	815 (0.48)	
Breast disease status			< 0.001

Characteristic	Controls *N* (%)	Cases *N* (%)	*p*-value*
No	1316 (0.78)	1153 (0.68)	
Yes, 1 biopsy	257 (0.15)	351 (0.21)	
Yes, 2 or more biopsies	114 (0.07)	183 (0.11)	
Unopposed estrogen usage			0.77
Never	1081 (0.64)	1053 (0.63)	
Past	206 (0.12)	213 (0.13)	
Current < 5 years	78 (0.05)	74 (0.04)	
Current 5–10 years	81 (0.05)	80 (0.05)	
Current greater than 10 years	239 (0.14)	264 (0.16)	
Estrogen plus progesterone usage			< 0.001
Never	1174 (0.70)	1033 (0.61)	
Past	133 (0.08)	138 (0.08)	
Current < 5 years	147 (0.09)	169 (0.10)	
Current 5–10 years	119 (0.07)	169 (0.10)	
Current greater than 10 years	114 (0.07)	178 (0.11)	
Statin usage			0.60
No	1555 (0.92)	1564 (0.93)	
Yes	132 (0.08)	123 (0.07)	
General health rating			0.02
Fair/poor	383 (0.23)	316 (0.19)	
Good	681 (0.41)	739 (0.44)	
Very good	513 (0.31)	509 (0.30)	
Excellent	104 (0.06)	117 (0.07)	
Gail risk score > 1.67			< 0.001
No	876 (0.52)	723 (0.43)	
Yes	811 (0.48)	964 (0.57)	
Statin type			0.15
None	1555 (0.92)	1564 (0.93)	
Hydrophilic	35 (0.02)	46 (0.03)	
Lipophilic	97 (0.06)	77 (0.05)	

*Chi-square test

Table 2

Traditional risk factor model

Variable	Odds ratio	*p*-value
Gail score > 1.67	1.43	< 0.001
E+P < 5 years	1.40	0.002
E+P >= 5 years	1.92	< 0.001
WaistCat > 88 cm	1.27	0.004
Benign breast disease—yes	1.44	< 0.001
Percent energy from fat > 30	1.16	0.048
Statin status—yes	0.46	0.001
WaistCat > 88 cm × statin status—yes	2.30	0.005
E+P < 5 years × statin status—yes	1.41	0.344
E+P >= 5 years × statin status—yes	4.33	0.003

Table 3

Candidate statin pathway gene SNP×Statin marginally significant results

SNP	Gene	Genotype	No statin use			Ever used statins			*p* int
			N	OR*	95% CI	*N*	OR*	95% CI	
rs9282564	ABCB1	AA	2546	1.00		203	0.42	(0.26,0.67)	0.04
		GA/GG	573	0.87	(0.72,1.05)	52	0.77	(0.32,1.85)	
rs1529711	CARM1	GG	2235	1.00		186	0.36	(0.21,0.60)	0.01
		AG/AA	882	0.93	(0.79,1.09)	69	0.74	(0.32,1.70)	

*Adjusted for the following significant variables: Gail score > 1.67, estrogen plus progestin (E+P) use < 5 years, E+P use >= 5 years, waist > 88 cm, benign breast disease (yes), % energy from fat > 30 g/day, statin status (yes), waist > 88 cm × statin status, E+P < 5 years × statin status, E+P >= 5 years × statin status