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Interactions between breast cancer susceptibility loci and menopausal hormone therapy in relationship to breast cancer in the Breast and Prostate Cancer Cohort Consortium

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CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

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Abstract

Purpose—Current use of menopausal hormone therapy (MHT) has important implications for postmenopausal breast cancer risk, and observed associations might be modified by known breast cancer susceptibility loci. To provide the most comprehensive assessment of interactions of prospectively-collected data on MHT and 17 confirmed susceptibility loci with invasive breast cancer risk, a nested case-control design among eight cohorts within the NCI Breast and Prostate Cancer Cohort Consortium was used.

Methods—Based on data from 13,304 cases and 15,622 controls, multivariable-adjusted logistic regression analyses were used to estimate odds ratios (OR) and 95% confidence intervals (CI). Effect modification of current and past use was evaluated on the multiplicative scale. P-values $<1.5\times10^{-3}$ were considered statistically significant.

Results—The strongest evidence of effect modification was observed for current MHT by 9q31-rs865686. Compared to never users of MHT with the rs865686 GG genotype, the association between current MHT use and breast cancer risk for the TT genotype (OR=1.79, 95% CI 1.43 – 2.24; $P_{interaction}=1.2\times10^{-4}$) was less than expected on the multiplicative scale. There are no biological implications of the sub-multiplicative interaction between MHT and rs865686.

Conclusions—Menopausal hormone therapy is unlikely to have a strong interaction with the common genetic variants associated with invasive breast cancer.

Keywords

Breast cancer; menopausal hormone therapy; genetic variation

INTRODUCTION

Current use of combined menopausal hormone therapy (MHT) has important implications for breast cancer risk due to altered exposure to sex steroid hormones during and after the menopausal transition [1–4]. In observational studies, the increased risk associated with MHT use dissipates within two years of cessation [1, 2, 4, 5], whereas some longer-term risk elevation was observed in the Women's Health Initiative (WHI) randomized, placebo

controlled trial [6]. Timing of initial use of MHT relative to the menopausal transition ("gap time") also appears to modify the association with risk; women who start using MHT within 5 years of menopause were at higher risk of developing breast cancer than those who started using MHT after 5 years or more since menopause [7]. The association between use of estrogen only therapy and breast cancer risk is unclear. In U.S. observational studies, estrogen-only therapy was not associated with risk of breast cancer [4] and, in fact, the WHI trial found suggestive evidence of a decreased risk of breast cancer among women in the estrogen only arm during the intervention phase of the trial [8], which became significant with additional follow-up [6]. However, results from the Million Women Study in the U.K. showed a positive association between current users of estrogen alone and risk of breast cancer [1]. Higher prevalence of obesity in the U.S. compared to the U.K. might partially explain the differences in associations with MHT, because associations of both combined and estrogen-alone MHT are stronger in leaner women compared to obese women [1, 2].

Although there have been significant declines in use of MHT therapy since the publication of the WHI combined MHT trial results in 2002 [9], women in the U.S. and Europe continue to use MHT [10]. Given its effectiveness in controlling menopausal symptoms, it would be helpful to identify characteristics of women that have an elevated breast cancer risk due to their MHT use. Genome-wide association studies (GWAS) [11–17] have led to the identification and confirmation of a number of single nucleotide polymorphisms (SNPs) associated with breast cancer risk. The interaction of these variants with MHT has been examined in a few large studies [18–25]; however, no SNP-MHT interactions have been verified for breast cancer.

We aimed to evaluate interactions of MHT use and breast cancer susceptibility loci in relation to risk of breast cancer among eight cohorts within the NCI Breast and Prostate Cancer Cohort Consortium (BPC3) using a nested case-control design. Previous efforts to examine interactions in the BPC3 have included MHT use at the time of the baseline questionnaire [22]. Because breast cancer risk is elevated primarily among women currently using combined MHT, in the present analysis we evaluated MHT use reported in the questionnaire just prior to diagnosis for the cases and just prior to a matched reference date for the controls, when possible, and controlled for the time interval between the date the questionnaire was completed and the reference date.

METHODS

Study population

The BPC3 consists of eight prospective cohorts from Europe, Australia, and the U.S. that have DNA samples and extensive questionnaire information collected from study participants before breast cancer diagnoses [26]. The BPC3 studies include the European Prospective Investigation into Cancer and Nutrition (EPIC) [27], the Women's Health Initiative (WHI) [28], the Melbourne Collaborative Cohort Study (MCCS) [29], the Nurses' Health Study I (NHSI) [30], the Nurses' Health Study II (NHSII) [31], the Women's Health Study (WHS) [32], the American Cancer Society's Cancer Prevention Study II Nutrition Cohort (CPS-II NC) [33], the Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial (PLCO) [34], and the Multi-Ethnic Cohort (MEC) [35] (Supplemental Table 1). Each cohort

provided DNA samples and survey-based data from study participants using a nested case-control design. Cases were study participants who were diagnosed with invasive breast cancer during the study follow-up. Cancer diagnoses were confirmed by medical records and/or cancer registries (the exact method varied among cohorts). Study participants were considered eligible controls if they were free of breast cancer until the follow-up time for the matched case subject. Matching criteria varied between studies, but age at baseline and menopausal status at baseline were common for all. Relevant institutional review boards for each cohort approved the project and informed consent was obtained from all study participants.

Genotyping, SNP selection, and genotype variables

Genotyping was performed using TaqMan assays (Applied Biosystems, Foster City, CA, USA) as specified by the manufacturer. Genotyping of the breast cancer cases and controls was performed in four laboratories (German Cancer Research Center (DKFZ), University of Southern California, U.S. National Cancer Institute (NCI), and Harvard School of Public Health). Laboratory personnel were blinded to whether samples were duplicates or from cases or controls. The concordance of duplicate (~8%) was greater than 99.9%.

The SNPs selected for these analyses (Supplemental Table 2) were associated with breast cancer risk at the threshold of genome-wide statistical significance (per allele p-values $<5\times10^{-8}$) and had a nominal level of statistical significance (per allele p-values <0.05) in our study (17 of 31 available genotyped SNPs met these criteria). For two loci, data for the original top SNP were not available and data from a surrogate SNP in complete linkage disequilibrium ($r^2=1$ in HapMap CEU) with the published SNP were used; these were rs4415084 (surrogate rs920329) and rs999737 (surrogate rs10483813) (Supplemental Table 2). In all analyses, the SNPs were modelled as counts of minor alleles.

MHT variables

Data on MHT use from the questionnaires just prior to diagnosis for cases and to the matched reference date for controls were harmonized centrally across the cohorts (median time between questionnaire and reference date is provided in Supplemental Table 1). We collected information on status (current, former, never), duration (≤2 years and >2 years), and time between menopause and first use of hormones (≤5years and >5years) for any hormone therapy, combined estrogen plus progesterone therapy, and estrogen-only therapy. For PLCO and EPIC, information on MHT status (current, former, never) was available only at baseline, and the questionnaires for these studies did not distinguish between combined and estrogen only therapies. Similarly, for MCCS, MHT use was not collected by type of therapy in the baseline or follow-up surveys (Supplemental Table 1).

Data filtering and statistical analysis

Study participants were excluded from the analytical dataset if they were premenopausal at reference date, or self-described as non-white. We also excluded subjects for which less than 90% of the SNPs had been successfully genotyped. The allele distribution of each SNP was tested for Hardy-Weinberg equilibrium among the controls of each study; SNPs with distributions out of Hardy-Weinberg equilibrium (p<0.001) were excluded from analysis.

We estimated odds ratios (ORs) and 95% confidence intervals (CI) for genotypes, MHT, and their combinations using unconditional logistic regression models. Since the unconditional models have better power than the conditional ones we decided to break the matching and include the matching factors as adjustment variables instead. Hence, the main effects analyses of MHT were minimally adjusted for age at reference, time interval between date of questionnaire and date at reference, cohort and country within EPIC. They were also multiple variable-adjusted. The multiple variable-adjusted models included age at menarche, number of full-term pregnancies, BMI, height, first-degree family history of breast cancer, smoking status, alcohol consumption, and age at menopause. The main effects analyses of genotypes were minimally-adjusted as indicated above and the interaction models were all multiple variable-adjusted. Possible interactions between MHT use and genotypes in relation to breast cancer risk were evaluated on the multiplicative scale. Deviations were assessed by comparing a logistic regression model with and without a product interaction term for MHT use and genotype. In the interaction analyses, the genotypes were modelled as counts of minor alleles, the MHT variables were categorized, and the reference group consisted of never users or low duration users with the minor allele genotype.

Between-study heterogeneity was evaluated first for all risk factors by testing the study*risk factor interaction term [36]. Risk factors whose associations varied by study were then added to the multiple variable-adjusted model as an interaction term with study. Using this multiple variable-adjusted model, we then applied the likelihood ratio test to assess between-study heterogeneity for MHT use. MHT associations that varied by study were addressed by including a study*MHT*SNP variable in all subsequent models.

In sensitivity analyses, we also examined the interactions between MHT and SNPs using the baseline exposure assessment for MHT (similar to previously performed BPC3 interaction analyses [22]). As a comparison, we also provided multiple variable-adjusted ORs and 95% CIs among the women who had MHT use information captured five years or less from date at reference. Because there is some evidence that the association between MHT and breast cancer risk might be limited to women with a low BMI [1, 2], we also conducted a sensitivity analysis in which we restricted the interaction analyses to women with a BMI of 22.4 kg/m^2 or lower.

We computed the P-value threshold for statistical significance ($P<1.5\times10^{-3}$) based on 34 comparisons based on 17 SNPs and 2 non-genetic factors (combined estrogen and progesterone therapy and estrogen only therapy, ever-use and duration of use were not considered as independent tests) [37]. All statistical tests were two-sided and all statistical analyses were performed with SAS version 9.2.

RESULTS

The full BPC3 pooled dataset included 45,570 women; after exclusions, data were available on 28,926 postmenopausal participants, including 13,304 invasive breast cancer cases and 15,622 controls. Among these women, 19% were currently using combined MHT at reference and 16% were using estrogen only therapy, although there was substantial variation across studies (Supplemental Table 1). The mean BMI was 27 kg/m^2 (standard

deviation=5), 10% had a first-degree family history of breast cancer, and 51% went through menopause at age 50 years or older (Supplemental Table 1).

The associations of SNPs with breast cancer risk were consistent in their direction and magnitude with previous reports (Supplemental Table 2, the reference genotype varies from that in Table 2).

The ORs from the minimally-adjusted and the multiple variable-adjusted main effect models for any and combined MHT use in relation to breast cancer risk differed by more than 10%, thus estimates mentioned below and those of the interaction analyses are fully adjusted (Table 1). Statistically significant between-study heterogeneity (p-values for interaction terms for individual studies <0.005) was detected for several of the MHT use variables. By removing individual studies, we identified WHS, EPIC and PLCO as the source of heterogeneity for any MHT use. WHS influenced the heterogeneity for use of combined and estrogen only therapy, and EPIC together with PLCO strongly affected duration of any MHT use. Therefore, in the SNP*MHT interaction models using data from all cohorts, we added interaction variables for these individual cohorts and MHT use.

Current use of any type of MHT was associated with a higher risk of breast cancer compared to women who never took MHT (Table 1). This increased risk appeared to be driven by current use of combined MHT (OR=2.00, 95% CI 1.71 – 2.34), although there was also a slightly higher risk for use of estrogen-only therapy (OR=1.20, 95% CI 1.04 – 1.38). Among MHT users, compared to less than 2 years of use, use of MHT for >2 or more years was associated with a higher risk of breast cancer. Use of any type of MHT initiated more than 5 years after the onset of menopause was associated with a lower risk of breast cancer, compared to use that commenced within 5 years of menopause among users (Table 1).

We examined interaction of 17 breast cancer SNPs and MHT use in relation to breast cancer risk (Supplemental Table 3). Interaction between rs865686 and use of any type of MHT had the lowest p-value (Table 2). Compared to never users of MHT with the rs865686 GG genotype, current MHT users with the TT genotype had a 79% higher risk of developing breast cancer (OR=1.79, 95% CI 1.43– 2.24); and this was less than expected assuming the MHT and SNP ORs multiply (p-value for interaction=1.2×10^{-4}). There was no between-study heterogeneity for this finding (p=0.02; based on the threshold 0.05/8 studies). Among women with a BMI between 18.1 and 22.4 kg/m^2, the interaction between MHT status and rs865686 was similar (p-value for interaction=2.2×10^{-5}; data not otherwise shown). The interaction between any type of MHT and rs865686 was limited to risk of ER+ breast cancer (ER+ cases=3,695) (Table 3), but not risk of ER-breast cancer (ER-cases=472).

The interaction between use of any MHT and rs865686 was similar (p-value for interaction=1.6×10^{-4}) after exclusion of data from PLCO, EPIC, and MCCS, studies that did not have complete information on type of MHT use. Because we were concerned about misclassification of current use of MHT over the follow-up period, we examined more closely the influence of baseline data, data collected just before reference date, and controlling for the difference between date of questionnaire and reference among the six studies (CPS-II NC, MCCS, MEC, NHS, WHI, and WHS) that had both baseline and

follow-up data (Supplemental Table 4). There was no evidence of interaction between use of any type of MHT and rs865686 when only baseline MHT data were used. Interaction ORs based on MHT data queried on follow-up questionnaires and specifically limited to five or fewer years prior to the reference date (Supplemental Table 4) were statistically significant and similar to those that were based on all available data including a combination of both baseline and follow-up data and controlled for the elapsed time between questionnaire and reference date (Table 2).

DISCUSSION

In a pooled analysis of 13,304 invasive breast cancer cases and 15,622 controls, we found suggestive evidence that the joint association of current use of any MHT and rs865686 with breast cancer risk was less than expected on the multiplicative scale. Although the main effect results for MHT duration were influenced by between-study heterogeneity, the interaction results were consistent across the eight cohorts.

The SNP, rs865686, located in an intragenic region at 9q31.2, was reported initially to be associated with a lower breast cancer risk overall ($OR_{per\text{-}allele}$=0.89, 95% CI 0.85 – 0.92) [38] and confirmed subsequently by the Breast Cancer Association Consortium (BCAC) as an ER+ susceptibility SNP ($OR_{per\text{-}allele}$=0.90, 95% CI 0.88 – 0.91) [39] in women of European ancestry. In our study of women with data on MHT, the main effect of rs865686 was consistent with these original results ($OR_{per\text{-}allele}$=0.91, 95% CI 0.88 – 0.94). The region immediately surrounding the SNP is a gene desert and the nearest annotated genes are *KLF4* and *RP11-505C13.1*, located at least 600kb from rs865686. There is no published functional information about the surrounding region tagged by rs865686.

Although other studies have examined interactions of other breast cancer susceptibility SNPs with other breast cancer risk factors [20, 21, 40–42], only BCAC examined interactions between MHT and 9q31-rs865686 [21, 40]. Using both a traditional analytical approach of interactions of known susceptibility loci on the multiplicative scale [40] and a genome-wide examination of novel loci based on gene-environment interactions [21], these studies did not find evidence of interactions between MHT and 9q31-rs865686 ($p \geq 10^{-3}$) among approximately 70,000 study participants from 21 case-control studies and 2 prospective cohort studies. It should be pointed out that the MCCS cohort was included both in the present study as well as in the BCAC, giving rise to a slight overlap of the samples. However, with the exclusion of MCCS from this study our results changed only marginally. Differences in results might be due to chance or differences in exposure assessment. 9q31-rs865686 did not interact with other breast cancer risk factors in previous cohort or case-control studies [20, 21, 40–42], other than perhaps mammographic density, but results across studies were inconsistent [43–45]. Previous studies have reported interactions between MHT and other breast cancer susceptibility SNPs, including 2q35-rs13387042, *NRIP1*-rs2823093, *RAD51L1*-rs999737, and *FGFR2* SNPs [20, 40–42]; however, these results might have been spurious because they were not replicated in our study or any other published studies.

As gene-environment interactions are expected to be moderate, large sample sizes are needed to detect them [46]. However, pooling data can be a trade-off between data quantity

and the specificity of the exposure information. Not all studies in the present analysis distinguished between type of MHT use, and our strongest finding was an interaction with use of any type of MHT, which might suggest it is artifactual. However, the interaction between any type of MHT and 9q31-rs865686 was similar for all studies and for studies with complete information on type, and we observed a borderline statistically significant interaction between estrogen only therapy and 9q31-rs865686. The BPC3 has been one of the largest efforts up to date using data only from prospective studies. Still, one of its weaknesses is limited power to detect interactions, due to insufficient sample size, especially after multivariable adjustment. We chose to investigate the possible interactions between breast cancer susceptibility SNPs and MHT use using a common reference group to elucidate any effect modification on the multiplicative scale after accounting for possible confounders. In particular, it should be noted that, given that the association of MHT use with breast cancer risk diminishes quickly after MHT cessation, accounting for time between questionnaire and reference date was of major importance in our analyses.

Our study summarizes the work on interaction of MHT use and breast cancer SNPs carried out within the framework of the BPC3. As mentioned above, sample size is crucial when investigating gene-environment interactions and our results need to be replicated in an independent sample. However, it appears unlikely that there is substantial variation in the breast cancer risk associated with MHT by the common breast cancer susceptibility SNPs. Therefore, it is unlikely that these SNPs would be clinically useful in delineating MHT users at high risk of breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Minimally-adjusted and multiple variable-adjusted[1] odds ratios (OR) and 95% confidence intervals (CI) for the associations of menopausal hormone therapy (MHT) with breast cancer risk in the NCI Breast and Prostate Cancer Cohort Consortium

MHT Variables	Cases[2] No. (%)	Controls[2] No. (%)	Minimally-adjusted OR (95% CI)	p-value	Multivariable-adjusted OR (95% CI)	p-value
Use of any MHT prior to reference						
Never	1924 (36%)	2508 (45%)	1.00		1.00	
Former	1700 (31%)	1670 (30%)	1.25 (1.17–1.34)	7.8×10^{-10}	1.30 (1.18–1.43)	1.9×10^{-7}
Current	1778 (33%)	1452 (26%)	1.37 (1.27–1.47)	2.5×10^{-17}	1.45 (1.30–1.61)	5.3×10^{-12}
Use of combined MHT prior to reference						
Never	2215 (60%)	2686 (74%)	1.00		1.00	
Former	720 (20%)	568 (16%)	1.43 (1.31–1.57)	2.4×10^{-14}	1.57 (1.38–1.79)	1.9×10^{-11}
Current	729 (20%)	395 (11%)	1.81 (1.63–2.02)	5.4×10^{-27}	2.00 (1.71–2.34)	4.0×10^{-18}
Use of estrogen only MHT prior to reference						
Never	1819 (52%)	1954 (54%)	1.00		1.00	
Former	973 (28%)	1009 (28%)	1.09 (1.00–1.19)	0.94	1.13 (1.01–1.27)	0.04
Current	717 (20%)	654 (18%)	1.17 (1.06–1.30)	0.02	1.20 (1.04–1.38)	0.01
Duration of use of any MHT use prior to reference						
≤2 years	1565 (45%)	1686 (54%)	1.00		1.00	
>2 years	1913 (55%)	1436 (46%)	1.37 (1.27–1.48)	1.0×10^{-16}	1.15 (1.01–1.32)	0.037
Duration of use of combined MHT use prior to reference						
≤2 years	1029 (71%)	799 (83%)	1.00		1.00	
>2 years	420 (29%)	164 (17%)	1.84 (1.66–2.04)	1.0×10^{-31}	1.48 (1.19–1.84)	3.7×10^{-4}
Duration of use of estrogen only MHT use prior to reference						
≤2 years	1099 (65%)	1114 (67%)	1.00		1.00	
>2 years	591 (35%)	549 (33%)	1.13 (1.03–1.25)	9.5×10^{-3}	1.00 (0.83–1.20)	0.99
Years between menopause and first use of any MHT						
≤5 years	279 (57%)	204 (45%)	1.00		1.00	
>5 years	212 (43%)	252 (55%)	0.73 (0.62–0.86)	2×10^{-4}	0.61 (0.47–0.81)	4.5×10^{-4}

[1] Multiple variable adjusted models included age, cohort/sub-cohort, time interval between date of questionnaire and date at reference, full-term pregnancy, body mass index, height, first-degree family history, active smoking status, alcohol consumption, age at menopause, and cohort*exposure variables as needed.

[2] The total number of subjects includes only those with non-missing values for the adjustment variables.

Table 2

Multivariable-adjusted[1] odds ratios (OR) and 95% confidence intervals (CI) for the associations of the menopausal hormone therapy (MHT) with breast cancer risk by breast cancer susceptibility locus, rs865686, in a subset of the NCI Breast and Prostate Cancer Cohort Consortium

MHT Variables	Cases[2] No. (%)	Controls[2] No. (%)	Multivariable-adjusted[1] OR (95% CI) by Genotype			p-value for interaction
			GG	TG	TT	
Use of any MHT prior to reference						
Never	1790 (34%)	2102 (41%)	1.00	1.48 (1.20–1.83)	1.26 (1.03–1.55)	
Former	1674 (32%)	1626 (32%)	1.33 (1.00–1.76)	1.65 (1.34–2.04)	1.80 (1.45–2.23)	
Current	1730 (33%)	1387 (27%)	2.15 (1.58–2.91)	1.90 (1.53–2.37)	1.79 (1.43–2.24)	1.2×10^{-4}
Use of combined MHT prior to reference						
Never	2211 (61%)	2669 (74%)	1.00	1.26 (1.05–1.52)	1.22 (1.01–1.46)	
Former	716 (20%)	559 (15%)	1.54 (1.07–2.20)	1.70 (1.35–2.16)	2.12 (1.65–2.72)	
Current	726 (20%)	393 (11%)	1.95 (1.30–2.93)	2.26 (1.73–2.97)	2.46 (1.85–3.26)	0.25
Use of estrogen only MHT prior to reference						
Never	1815 (52%)	1935 (54%)	1.00	1.49 (1.20–1.85)	1.26 (1.02–1.56)	
Former	967 (28%)	1005 (28%)	1.23 (0.89–1.70)	1.51 (1.20–1.90)	1.49 (1.17–1.88)	
Current	717 (20%)	652 (18%)	1.74 (1.17–2.57)	1.66 (1.28–2.15)	1.40 (1.07–1.83)	0.05
Duration of use of any MHT use prior to reference						
≤2 years	1599 (47%)	1597 (53%)	1.00	1.11 (0.81–1.53)	1.12 (0.82–1.54)	
>2 years	1805 (53%)	1416 (47%)	1.10 (0.76–1.61)	1.28 (0.94–1.74)	1.29 (0.95–1.76)	0.023
Duration of use of combined MHT use prior to reference						
≤2 years	1038 (72%)	790 (83%)	1.00	1.63 (0.95–2.82)	1.56 (0.91–2.69)	
>2 years	404 (28%)	162 (17%)	2.16 (1.17–4.00)	1.81 (1.08–3.04)	2.28 (1.35–3.85)	0.77
Duration of use of estrogen only MHT use prior to reference						
≤2 years	1111 (66%)	1094 (66%)	1.00	1.35 (0.86–2.11)	1.33 (0.86–2.07)	
>2 years	573 (34%)	563 (34%)	1.16 (0.70–1.94)	1.28 (0.84–1.95)	1.17 (0.77–1.80)	0.50
Years between menopause and first use of any MHT						
>5 years	210 (43%)	247 (55%)	1.00	1.47 (0.82–2.65)	1.12 (0.62–1.99)	
≤5 years	277 (57%)	200 (45%)	2.25 (0.96–5.27)	1.93 (1.07–3.47)	2.13 (1.17–3.87)	0.68

[1]Multiple variable adjusted models included age, cohort/sub-cohort, time interval between date of questionnaire and date at reference, full-term pregnancy, body mass index, height, first-degree family history, active smoking status, alcohol consumption, age at menopause, and cohort*exposure variables as needed.

[2]The total number of subjects includes only those with non-missing values for the adjustment variables.