Genetic modifiers of menopausal hormone replacement therapy and breast cancer risk: a genome–wide interaction study

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Women using menopausal hormone therapy (MHT) are at increased risk of developing breast cancer (BC). To detect genetic modifiers of the association between current use of MHT and BC risk, we conducted a meta-analysis of four genome-wide case-only studies followed by replication in 11 case–control studies. We used a case-only design to assess interactions between single-nucleotide polymorphisms (SNPs) and current MHT use on risk of overall and lobular BC. The discovery stage included 2920 cases (541 lobular) from four genome-wide association studies. The top 1391 SNPs showing \( P \) values for interaction \( (P_{\text{int}}) < 3.0 \times 10^{-3} \) were selected for replication using pooled case–control data from 11 studies of the Breast Cancer Association Consortium, including 7689 cases (676 lobular) and 9266 controls. Fixed-effects meta-analysis was used to derive combined \( P_{\text{int}} \). No SNP reached genome-wide significance in either the discovery or combined stage. We observed effect modification of current MHT use on overall BC risk by two SNPs on chr13 near POMP (combined \( P_{\text{int}} \leq 8.9 \times 10^{-6} \)), two SNPs in SLC25A21 (combined \( P_{\text{int}} \leq 4.8 \times 10^{-5} \)), and three SNPs in PLCG2 (combined \( P_{\text{int}} \leq 4.5 \times 10^{-5} \)). The association between lobular BC risk was potentially modified by one SNP in TMEFF2 (combined \( P_{\text{int}} \leq 2.7 \times 10^{-5} \)), one SNP in CD80 (combined \( P_{\text{int}} \leq 8.2 \times 10^{-6} \)), three SNPs on chr17 near TMEM132E (combined \( P_{\text{int}} \leq 2.2 \times 10^{-6} \)), and two SNPs on chr18 near SLC25A52 (combined \( P_{\text{int}} \leq 4.6 \times 10^{-5} \)). In conclusion, polymorphisms in genes related to solute transportation in mitochondria, transmembrane signaling, and immune cell activation are potentially modifying BC risk associated with current use of MHT. These findings warrant replication in independent studies.
in 2005 reported an odds ratio (OR) of 1.39 (95% CI 1.12–1.72) for the association between the use of combined estrogen–progestogen therapy and BC risk, whereas the respective OR for use of estrogen-monotherapy was 1.16 (95% CI 1.06–1.28) (Shah et al. 2005). Also, differences in histology have been observed, with a stronger increase in the risk for lobular and tubular BCs compared with ductal BC (Flesch-Janys et al. 2008, Bakken et al. 2011).

Understanding of the role of female sex hormones in breast carcinogenesis has already led to the development of therapeutic strategies such as the adjuvant endocrine therapy for estrogen-receptor-positive BC (Smith & Dowsett 2003). By investigating genetic modifiers of MHT-associated BC, the underlying mechanisms could be further elucidated. The detection of genes involved in hormone-related breast carcinogenesis could lead to new strategies for BC prevention and treatment. Knowledge of genetic modifiers could also contribute to safer use of MHT, as the individual risk of developing BC when using MHT may vary depending on the genetic background.

Previous studies investigating the interactions between single-nucleotide polymorphisms (SNPs) and use of MHT regarding BC risk predominantly pursued a candidate-gene approach. Most of the reported interactions have not been followed up in further studies (Lee et al. 2011, Hein et al. 2012, Justenhoven et al. 2012). The possible interaction with the variants of the known genetic susceptibility loci for BC in FGFR2 has not been clearly confirmed in subsequent studies (Kawase et al. 2009, Prentice et al. 2009, Rebbeck et al. 2009, Travis et al. 2010, Campa et al. 2011, Nickels et al. 2013). We previously failed to replicate the most significant interaction with MHT use observed for 2q36.3 in a genome–wide interaction study using a case-only approach (Hein et al. 2013).

We here have expanded our previous work (Hein et al. 2013) and conducted a meta-analysis of four case-only genome-wide gene–environment interaction studies for overall as well as for lobular BC risk. We then evaluated the top 1391 SNPs by case–control analyses using data from 11 studies by researchers participating in the Breast Cancer Association Consortium (BCAC; http://ccge.medschl.cam.ac.uk/consortia/bcac/index.html).

Study population of case-only genome-wide studies

Under the assumption that the genetic and environmental factors are not associated in the population from which the cases were drawn, case-only studies provide a powerful and efficient way to detect gene–environment interactions (Piezorsch et al. 1994). We conducted a meta-analysis of four studies with quality control-checked genome-wide data and information on current MHT use: the Mammary Carcinoma Risk Factor Investigation (MARIE) from Germany (Flesch-Janys et al. 2008), the Singapore and Sweden Breast Cancer Study (SASBAC; Wedren et al. 2004), the Helsinki Breast Cancer Study (HEBCS; Kilpivaara et al. 2004), and the Nurses’ Health Study (NHS) from the USA (Hunter et al. 2007). Details on all studies included in the discovery as well as replication stage can be found in Supplementary Table 1, see section on supplementary data given at the end of this article. In total, these studies contributed 2920 cases (541 cases with lobular tumors) to the meta-analysis.

Briefly, the MARIE study is a population-based case–control study of postmenopausal women aged 50–74 years, carried out in two regions of Germany with the incident cases diagnosed during 2001–2005 and controls matched by birth year and study region (Flesch-Janys et al. 2008). Initially, 800 MARIE cases with a known age at menopause were randomly selected for genotyping, with lobular cases oversampled (Hein et al. 2013). After quality control checks, a total of 742 MARIE cases were included in the case-only genome-wide association analysis, of which 279 were lobular cases. SASBAC is a subset of a Swedish nationwide population-based case–control study (Wedren et al. 2004). The cases were incident BC cases diagnosed during 1993–1995 identified via the six regional cancer registries in Sweden, to which reporting is mandatory. Overall, 773 cases (36 lobular tumors) were included in the case-only genome-wide association analysis (Li et al. 2011). A further 344 postmenopausal cases (88 lobular tumors) were contributed by the hospital-based Finnish study HEBCS. In HEBCS, cases included both unselected BC and familial BC patients recruited at the Helsinki University Central Hospital, 1997–2004 (Kilpivaara et al. 2004). The NHS cohort was established in 1976 and comprised 121 700 female registered nurses. In 1989–1990, 32 826 participants donated a blood sample. Of this sub-cohort 1061 participants of European descent with incident postmenopausal invasive BC (138 lobular) were included in the case-only genome–wide association analysis (Hunter et al. 2007). All subjects were of European ancestry.
Study populations used in the replication stage

SNPs selected from the case-only genome-wide association studies for replication were evaluated using seven population-based studies (five case–control studies (CECILE, GENICA, MARIE, PBCS, SASBAC), one case–cohort (MCCS), and one nested case–control study (UKBGS)), and four non-population-based studies (MCBCS, kConFab/AOCS, OFBCR, pKARMA), including in total 7689 cases (676 lobular) and 9266 controls participating in the BCAC. Studies from BCAC were included if participants were of European descent and if genotype information, information on MHT use, and information on reference age were available for at least 200 postmenopausal cases and 200 postmenopausal controls. A reference age of \( \geq 54 \) years was used as surrogate for defining the postmenopausal status if study-derived information on menopausal status was missing. Participants in SASBAC and MARIE were excluded if they had contributed already to the respective case-only genome-wide association studies. Additionally, cases in MCCS and pKARMA with prevalent BC at time of enrollment were excluded. The reference date for controls was the date of enrollment (MCCS) or date of interview (case–control studies). The reference date for cases was the date of BC diagnosis. The reference age was accordingly the age at reference date. In total, 7698 cases (676 lobular) and 9266 controls contributed to the replication analysis.

MHT exposure definition

Any type of MHT was taken into account when defining ever use of MHT. Only women using MHT more than 3 months were considered to be ever users. We defined
current use of MHT as use within the last 6 months before reference date. Harmonization and plausibility checks of MHT information were conducted centrally for all studies participating in BCAC (Nickels et al. 2013).

**Genotyping and quality control**

Genotyping was performed using the Illumina HumanMethylation450 BeadChip in the study and the Illumina HumanMethylation450 BeadChip in SASBAC (500 007 SNPs), HEBCS (510 067 SNPs), and NHS (540 000 SNPs). Genotyping in NHS was part of the Cancer Genetic Markers of Susceptibility (CGEMS) project. All studies provided quality control-checked genotype data.

SNPs selected for replication were genotyped on a custom Illumina iSelect genotyping array (iCOGS) that was designed by BCAC in collaboration with three other consortia (the Collaborative Oncological Gene–Environment Study, COGS) (Michailidou et al. 2013). After genotyping, the iCOGS data were centrally quality controlled, which led to exclusion of 56 SNPs selected for replication. We additionally excluded nine SNPs with minor allele frequency (MAF) < 0.05 in the replication dataset.

**Imputation**

All SNPs genotyped in the genome-wide studies, which were also contained in the HapMap phase II release 24 data, were used for imputation of additional genotypes using the software MACH 1.0.16 (Li et al. 2010). Employing the ‘autoflip’ option, the alleles are coded according to a unique reference scheme, so that the same allele was coded as reference in all four genome-wide case-only studies. For quality control of imputed data, imputed SNPs with MAF < 0.01 or $r^2 < 0.3$ were excluded from the analysis.

**SNP selection for replication**

A list of 1391 SNPs was generated based on the lowest $P_{int}$ (cutoff $P_{int} < 3.0 \times 10^{-5}$) derived from the analysis of multiplicative interaction between MHT and BC risk, after merging the results for overall and lobular BC. A total of 3277 SNPs were selected based on the interaction with overall BC and 1723 selected based on their association with lobular BC. These SNPs were filtered according to the criteria of MAF $\geq 0.05$, $P$ value $\geq 0.05$ for Cochran’s Q or $I^2 < 30\%$ and the availability of the respective SNP data in at least two case-only studies.

**Statistical analysis**

We tested for multiplicative SNP×MHT interactions on the genome-wide level (2.5 million SNPs) in case-only analysis using logistic regression with MHT use (current use codes as 1, never/past use coded as 0) as the outcome variable and the SNP as the explanatory variable. The SNP was assessed according to a log-additive genetic model, i.e. a 1 df test for trend by number of minor alleles (0, 1, or 2). Uncertainty of imputed SNPs was accounted for by using estimated genotype probabilities for imputed SNPs in the regression model. Covariates were not considered in the case-only analyses. These analyses were performed with the software ProbABEL version 0.1-2-plus (Aulchenko et al. 2010). Only genotyped SNPs that were also contained in the HapMap reference data and imputed SNPs were included in the case-only analyses. Analyses were performed for all cases as well as separately for lobular cases. As only individuals of European descent were included, the genomic inflation factor lambda was close to one (HEBCS $\lambda = 1.016$; MARIE $\lambda = 1.014$; SASBAC $\lambda = 1.009$) and, in case of NHS, there was also no indication of population stratification (Hunter et al. 2007). Therefore, the analyses were not corrected for population stratification. Combined results based on the four case-only analyses were obtained from a meta-analysis assuming a fixed effects model, using the software PLINK, version 1.07 (Purcell et al. 2007). Heterogeneity between studies was assessed using Cochran’s Q statistic and $I^2$ (Higgins & Thompson 2002).

For the replication analysis, data from 11 studies were pooled and analyzed using case–control logistic regression. These analyses were performed using SAS software, version 9.2. SNP×MHT interactions were evaluated by means of a log-likelihood ratio test, comparing models with and without a multiplicative interaction term between SNP (coded according to log-additive mode of inheritance) and current use of MHT. The models were adjusted for study, reference age, former use of MHT, and six principal components to account for population stratification. The models included also interaction terms between study design (non-population-based vs population-based) and current use of MHT as well as former use of MHT. These interaction terms were included to account for possible differences in the estimates of the MHT effect according to study design.

Results from the case-only meta-analysis and the replication were combined in a meta-analysis assuming a fixed effects model, using the package ‘meta’, version 2.1-2 (Schwarzer 2012) within the R software, version 2.15.0.
Linkage disequilibrium (LD) between selected SNPs was estimated in the control population of population-based studies using SNP_Tools, version 1.70 (Chen et al. 2009a), and Haploview, version 4.2 (Barrett et al. 2005).

The association between current MHT use and SNPs was assessed using data from all studies of the replication stage as well as solely population-based studies. We fitted a logistic regression model adjusted for study with current MHT use as the outcome.

To illustrate the modification of overall as well as lobular BC risk associated with current use of MHT by SNPs, the effect of current use of MHT was assessed in strata defined by the SNP genotype in pooled case–control data of the replication stage. The models were adjusted for study, reference age, former use of MHT, and the two previously described interaction terms to account for possible differences in the estimates of the MHT effect according to study design.

To further evaluate the effect of modification of current use of MHT by multiple modifying loci, a polygenic score was built for each individual. For the polygenic score, we included the genetic loci found to modify the association with current use of MHT at a significance level of $P_{\text{int}} < 5.0 \times 10^{-5}$ and selected one SNP per region based on the effect estimate. The allele increasing the effect of MHT on BC risk was used as the risk allele and the polygenic score was derived by summing up the risk alleles (0, 1 or 2) for each SNP. Separate scores were constructed for overall and lobular BC risk. To demonstrate the polygenic modifying effect, associations of current MHT use with BC risk were calculated stratified by score categories (roughly quintiles for all BCs and tertiles for lobular tumors). The respective logistic regression models were adjusted for study, reference age, former use of MHT, an interaction term between former use of MHT and study design (non-population-based vs population-based), and an interaction term between current use of MHT and study design.

**Results**

Characteristics of the patients participating in the studies included in the discovery stage and the replication stage are shown in Supplementary Tables 2 and 3, see section on supplementary data given at the end of this article. The prevalence of current use of MHT varied between 10 and 60%. The estimated OR for the marginal effect of current use of MHT in the population-based studies of the replication stage was 1.51 (95% CI 1.21–1.88) for overall BC and 1.83 (95% CI 1.34–2.47) for lobular BC, as displayed in Supplementary Figure 1.

The meta-analysis of the case-only genome-wide studies did not identify any SNP×MHT interaction at genome-wide significance level (see Supplementary Figures 2 and 3, respectively, for quantile-quantile (QQ) and Manhattan plots of the results). The strongest association was observed for rs3824418 located in an intronic region of TLE1 on 9q21.3 ($P_{\text{int}} = 6.7 \times 10^{-7}$).

Of the 1391 SNPs carried forward for replication, 944 were selected based on their $P_{\text{int}}$ for modification of overall BC risk associated with MHT, and 447 based on their $P_{\text{int}}$ for modification of lobular BC risk. Overall, seven SNPs showed effect modification of overall BC with combined $P_{\text{int}} < 5.0 \times 10^{-5}$, as well as seven SNPs with respect to lobular BC risk (Table 1). There was no strong association between the SNPs selected for follow-up and current use of MHT, as can be seen from QQ-plots in Supplementary Figure 4, see section on supplementary data given at the end of this article. When analyzing the whole sample of the replication stage, the SNPs showing strongest association with current use of MHT were rs12538442, located in an intronic region of DOCK4 on chromosome 1 ($P = 3.1 \times 10^{-4}$), and rs17738984, located on chromosome 17q22 ($P = 8.8 \times 10^{-4}$). The SNPs showing the strongest association with MHT use when restricting the sample to population-based studies were rs10924245 in KIF26B ($P = 1.6 \times 10^{-4}$) and rs2102354 in KCNN3 ($P = 7.7 \times 10^{-4}$), both located on chromosome 1.

Further information on SNPs, including their association with overall BC risk in the replication dataset and MAFs in the different study populations, can be found in Supplementary Table 4, see section on supplementary data given at the end of this article. The identified SNPs on each of the chromosomes 13, 14, 16, 17, and 18 are located in close proximity to each other and do not represent independent signals of genetic modification of the MHT effect. The respective LD plots can be found in Supplementary Figure 5.

For overall BC risk, two SNPs (rs9578047 and rs9579199) near POMP on chromosome 13 showed an interaction with current use of MHT with combined $P_{\text{int}} = 7.9 \times 10^{-6}$ and 7.6 $\times 10^{-6}$. SNP×MHT interactions with $P_{\text{int}}$ of similar magnitude were also observed with rs7148646 and rs848694 in SLC25A21 on chromosome 14 (combined $P_{\text{int}} = 1.2 \times 10^{-5}$ and 4.6 $\times 10^{-5}$) and three SNPs (rs7192724, rs17202296, and rs4888190) in PLCG2 on chromosome 16 (combined $P_{\text{int}} = 3.3 \times 10^{-6}$, 2.8 $\times 10^{-5}$, and 4.5 $\times 10^{-5}$) (Table 1). Associations between current use of MHT and overall BC risk stratified
<table>
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<th>Chr</th>
<th>Position (build 37)</th>
<th>RefSeq gene</th>
<th>Feature</th>
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<th>(P_{\text{int}})</th>
<th>Replication OR (95% CI)</th>
<th>(P_{\text{int}})</th>
<th>Combined(^b) OR (95% CI)</th>
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<td>1.24 (1.09–1.40)</td>
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<td>1.85 (1.22–2.81)</td>
<td>3.0 (\times 10^{-3})</td>
<td>1.88 (1.40–2.54)</td>
<td>3.4 (\times 10^{-5})</td>
</tr>
</tbody>
</table>

\(^a\)Fixed effects meta-analysis of results from four case-only GWAS.
\(^b\)Fixed effects meta-analysis of results from GWAS and replication analysis.
\(^c\)Adjusted for study, reference age, former use of MHT, interaction terms between study design (population-bases vs non-population-based), and former use and current of MHT, as well as genetic principal components.
by genotypes of these SNPs are displayed in Table 2. We did not observe significantly heterogeneous SNP×MHT interactions between studies that were pooled in the replication stage ($P_{\text{het}}$ ranging from 0.16 to 0.91). The respective forest plots are shown in Supplementary Figure 6, see section on supplementary data given at the end of this article.

We combined rs71486464_G, rs9579199_G, and rs7192724_G and constructed a polygenic score to assess BC risk associated with current use of MHT depending on the modifying genetic risk (number of risk modifying alleles) (Fig. 2A). For women with a low polygenic score of two or fewer risk-modifying alleles (16.7% of women), current use of MHT was not associated with an increased BC risk (OR = 1.04, 95% CI 0.87–1.25). Among women carrying three (30.9% of women) or four (34.2% of women) risk-modifying alleles, current use of MHT was associated with a significantly increased BC risk (OR = 1.36–1.80 respectively). The strongest association between current use of MHT and BC risk was observed for women carrying zero to four risk-modifying alleles (15.2% of women) (OR = 1.86, 95% CI 1.56–2.22), as expected.

With respect to lobular BC, the variant rs11680872 located in an intronic region of TMEFF2 on chromosome 2 showed a SNP×MHT interaction with combined $P_{\text{int}}$ = 2.9 × 10⁻⁵ (Table 1). Also, rs7648642 in CD80 on chromosome 3 modified MHT-associated lobular BC risk in both case-only and case–control analysis (combined $P_{\text{int}}$ = 5.1 × 10⁻⁶). The variants rs11654964, rs16970162, and rs11080292 located near TMEM132E on chromosome 17 yielded combined $P_{\text{int}}$ of 2.7 × 10⁻⁶, 8.6 × 10⁻⁶, and 9.3 × 10⁻⁶ respectively. Further SNP×MHT interactions were observed for rs6506940 and rs594334 near SLC25A52 on chromosome 18 (combined $P_{\text{int}}$ = 1.2 × 10⁻⁵ and 3.4 × 10⁻⁵ respectively) (Table 1). Table 2 shows the associations between current use of MHT and lobular BC risk in strata defined by genotypes of these SNPs. There was no significant heterogeneity by study regarding the estimates for SNP×MHT interactions ($P_{\text{het}}$ ranging from 0.22 to 0.94). The respective forest plots are shown in Supplementary Figure 7, see section on supplementary data given at the end of this article.

For lobular BC, a polygenic score was constructed by combining rs11680872_A, rs7648642_C, rs11654964_A, and rs6506940_A (Fig. 2B). Current use of MHT was not associated with increased lobular BC risk in women carrying zero to four risk-modifying alleles (15.2% of women, OR = 0.61, 95% CI 0.35–1.07), while the OR for lobular BC risk was 1.64 (95% CI 1.18–2.26) in the subgroup (25.5% of women) carrying five risk-modifying alleles. The association with current MHT use increased

### Table 2  Association between current use of menopausal hormone therapy (MHT) and overall as well as lobular breast cancer risk stratified by genotype

<table>
<thead>
<tr>
<th>SNP</th>
<th>Alleles*</th>
<th>Homozygous reference</th>
<th>Heterozygous</th>
<th>Homozygous coded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs9578047</td>
<td>A G</td>
<td>1.91 (0.96–2.50)</td>
<td>2.0 × 10⁻⁶</td>
<td>1.50 (1.30–1.72)</td>
</tr>
<tr>
<td>rs9579199</td>
<td>G A</td>
<td>1.92 (1.47–2.51)</td>
<td>1.8 × 10⁻⁶</td>
<td>1.50 (1.30–1.72)</td>
</tr>
<tr>
<td>rs7148646</td>
<td>G A</td>
<td>1.58 (1.39–1.80)</td>
<td>1.9 × 10⁻¹²</td>
<td>1.24 (1.08–1.43)</td>
</tr>
<tr>
<td>rs848694</td>
<td>G A</td>
<td>1.55 (1.37–1.75)</td>
<td>3.2 × 10⁻¹²</td>
<td>1.23 (1.06–1.43)</td>
</tr>
<tr>
<td>rs7192724</td>
<td>C G</td>
<td>1.10 (0.78–1.54)</td>
<td>5.9 × 10⁻¹⁰</td>
<td>1.25 (1.09–1.44)</td>
</tr>
<tr>
<td>rs17202296</td>
<td>C T</td>
<td>1.19 (0.88–1.62)</td>
<td>2.5 × 10⁻¹⁰</td>
<td>1.32 (1.15–1.51)</td>
</tr>
<tr>
<td>rs4888190</td>
<td>C G</td>
<td>1.22 (0.89–1.66)</td>
<td>2.1 × 10⁻¹⁰</td>
<td>1.36 (1.18–1.57)</td>
</tr>
<tr>
<td>Lobular breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs11680872</td>
<td>G A</td>
<td>1.33 (0.64–2.76)</td>
<td>4.5 × 10⁻¹¹</td>
<td>1.42 (1.04–1.94)</td>
</tr>
<tr>
<td>rs7648642</td>
<td>C A</td>
<td>3.05 (2.10–4.42)</td>
<td>4.1 × 10⁻⁹</td>
<td>1.62 (1.23–2.14)</td>
</tr>
<tr>
<td>rs11654964</td>
<td>C A</td>
<td>0.24 (0.06–1.04)</td>
<td>5.7 × 10⁻²</td>
<td>1.61 (1.18–2.19)</td>
</tr>
<tr>
<td>rs16970162</td>
<td>C G</td>
<td>0.33 (0.17–0.47)</td>
<td>1.5 × 10⁻¹</td>
<td>1.57 (1.14–1.27)</td>
</tr>
<tr>
<td>rs11080292</td>
<td>T C</td>
<td>0.38 (0.18–0.70)</td>
<td>2.0 × 10⁻¹</td>
<td>1.47 (1.06–2.03)</td>
</tr>
<tr>
<td>rs6506940</td>
<td>G A</td>
<td>0.94 (0.10–8.90)</td>
<td>9.6 × 10⁻¹</td>
<td>1.08 (0.72–1.61)</td>
</tr>
<tr>
<td>rs594334</td>
<td>C T</td>
<td>1.40 (0.24–7.98)</td>
<td>7.1 × 10⁻¹</td>
<td>1.03 (0.68–1.58)</td>
</tr>
</tbody>
</table>

*The coded allele was not necessarily the minor allele.

*Adjusted for study, reference age, former use of MHT, interaction between former use of MHT and study design (non-population-based vs population-based), and interaction between current use of MHT and study design.
increased risk of BC. Similar results were observed for women who were currently using MHT were at an intermediate risk among women with a polygenic score of three or four (16.7% of women included in the study) and was not associated with women with five to six risk-modifying alleles (18.2% of all women). The loci of the identified polymorphisms provide evidence of possible biological relevance for breast carcinogenesis. Two variants rs9579199 and rs9578047 close to FLT1 and POMP on chromosome 13 showed modifying effects on MHT-associated BC risk. FLT1 is a vascular endothelial growth factor receptor and involved in tumor angiogenesis (Fischer et al. 2008). So far, no association has been reported between tumor development and POMP, a proteasome maturation protein. The variants on chromosome 14 (rs7148646, and rs848694) lie in an intronic region of SLC25A21. SLC25A21 encodes an oxodicarboxylate carrier, which transports C5–C7 oxodicarboxylates across the inner membranes of mitochondria (Fiernmonte et al. 2001). Interestingly, the two SNPs, rs6506940 and rs594334, found to modify the risk of lobular BC are located near another mitochondrial carrier gene, SLC25A52, on chromosome 18. Estrogen has been reported to be an important regulator of mitochondrial function (Chen et al. 2009b) and results of this study suggest that mitochondria-related mechanisms may play a role in MHT-associated breast carcinogenesis. The association between MHT and BC was also modified by rs7192724, rs17202296, and rs4888190 located in intronic regions of PLCG2. PLCG2 is a member of the phosphoinositide-specific phospholipase C family and is involved in transmitting activation signals across the cell membranes predominantly of the B cells (Wang et al. 2000) as well as the natural killer cells (Tassi et al. 2005).

With respect to lobular BC, genetic variants of two transmembrane proteins were implicated, rs11680872 is located in an intron of TMEFF2, whose biological function is unclear but its promoter region has been commonly found to be hypermethylated in various cancers, including BC (Lin et al. 2011, Park et al. 2011). Three variants (rs11654964, rs16970162, and rs11080292) are near (23–32 kb 3’) TMEM132E, another transmembrane protein. We observed also an interaction with rs7648642, which lies in an intron of CD80 on chromosome 3. CD80 is known to play an important role in T cell activation (Bhatia et al. 2006), and its expression has been found to be decreased in peripheral blood of BC patients (Gong et al. 2012).

To account for differences by country with respect to types of preparations and dosages as well as different

### Discussion

Using a two-stage approach consisting of a meta-analysis of four case-only genome-wide association studies and a replication analysis of independent data from ten case-control studies, we attempted to identify SNPs that modify the effect of MHT use on BC risk. Despite our large sample size in both discovery and replication stages, we did not identify any SNPs that reached genome-wide significance. We observed three loci on chromosomes 13, 14, and 16 that modified MHT-associated overall BC risk in both the discovery and replication stage, with combined \( P_{\text{int}} < 5.0 \times 10^{-5} \). Additionally, four genomic loci on chromosomes 2, 3, 17, and 18 modified lobular BC risk associated with MHT use in both study stages at the same significance level.

When combining variants that modify the effect of current use of MHT in a polygenic score, current MHT use was associated with an 86% increased BC risk among women with five to six risk-modifying alleles (18.2% of all women included in the study) and was not associated with BC risk among women carrying two or fewer (16.7% of women). Women with a polygenic score of three or four who were currently using MHT were at an intermediate increased risk of BC. Similar results were observed for lobular BC risk. Given the observed interactions are confirmed, the polygenic score illustrates that even though the single detected interaction might be modest, the associated BC risk for a woman using MHT may be appreciably increased if she carries a large number of adverse risk-modifying alleles.

The loci of the identified polymorphisms provide evidence of possible biological relevance for breast carcinogenesis. Two variants rs9579199 and rs9578047 close to FLT1 and POMP on chromosome 13 showed modifying effects on MHT-associated BC risk. FLT1 is a vascular endothelial growth factor receptor and involved in tumor angiogenesis (Fischer et al. 2008). So far, no association has been reported between tumor development and POMP, a proteasome maturation protein. The variants on chromosome 14 (rs7148646, and rs848694) lie in an intronic region of SLC25A21. SLC25A21 encodes an oxodicarboxylate carrier, which transports C5–C7 oxodicarboxylates across the inner membranes of mitochondria (Fiernmonte et al. 2001). Interestingly, the two SNPs, rs6506940 and rs594334, found to modify the risk of lobular BC are located near another mitochondrial carrier gene, SLC25A52, on chromosome 18. Estrogen has been reported to be an important regulator of mitochondrial function (Chen et al. 2009b) and results of this study suggest that mitochondria-related mechanisms may play a role in MHT-associated breast carcinogenesis. The association between MHT and BC was also modified by rs7192724, rs17202296, and rs4888190 located in intronic regions of PLCG2. PLCG2 is a member of the phosphoinositide-specific phospholipase C family and is involved in transmitting activation signals across the cell membranes predominantly of the B cells (Wang et al. 2000) as well as the natural killer cells (Tassi et al. 2005).

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genotype platforms and laboratories, we used a meta-analysis to combine the results in the discovery stage and adjusted for study in the replication stage. Heterogeneity of estimates regarding MHT use between studies due to differences in the study design was in part accounted for by adding an interaction term between MHT use and study design in the regression models (Supplementary Figure 1). The sensitivity analysis restricted to solely population-based studies of the replication stage for selected SNP × MHT interactions did not yield substantially altered estimates for interaction (<7.5% for overall BC and <11.5% for lobular BC, Supplementary Table 5, see section on supplementary data given at the end of this article). Using the total study population for the replication stage, the study had 80% power to detect an interaction effect of 1.20, assuming an allele frequency of 20%, a marginal genetic effect of 1.15, and a marginal effect of current MHT use of 1.35. The power was reduced to 55% when restricting the sample to population-based studies. Furthermore, although the associations between current MHT use and BC risk observed in the single studies were heterogeneous, this was not the case for the SNP × MHT interactions (Supplementary Figures 6 and 7). In general, estimates for gene–environment interaction are unlikely to be affected by selection bias (Morimoto et al. 2003) and more likely to be underestimated in the presence of non-differential or differential misclassification (Garcia-Closas et al. 1999).

Most of the reported genetic modifiers of MHT-associated BC risk have so far not been followed up in further studies (Justenhoven et al. 2012). One exception is with respect to variants in FGFR2, as it is also a known BC susceptibility loci. Rebeck et al. (2009) reported that the association between combined estrogen–progestogen therapy and BC risk was modified by rs1219648 in postmenopausal women of European descent (Pint = 0.010). A study conducted in participants of the Women’s Health Initiative trial could not replicate this finding (Pint = 0.661) but observed an interaction with rs3750817 in FGFR2 (Pint = 0.033) (Prentice et al. 2009). A similar modifying effect of this SNP was also observed for estrogen-monotherapy (Pint = 0.046). The variants rs1219648 and rs3750817 are in moderate LD (r2 = 0.44, D’ = 1.00). However, we did not observe an interaction regarding BC risk with current use of any MHT and rs1219648 (Pint = 0.15) or rs3750817 (Pint = 0.23) in the genome-wide association study and the variants were not followed up in the replication stage. Similarly, no significant interactions were observed with FGFR2 variants in more recent studies (Campa et al. 2011, Andersen et al. 2012, Nickels et al. 2013).

Genome-wide studies of gene–environment interactions present challenges, as the required sample size may be inflated due to misclassification of environmental exposures and additional factors involved including effect size of gene–environment interaction and prevalence of environmental exposure(s) (Zondervan & Cardon 2004, Dempfle et al. 2008). To optimize power, we used the case-only approach in the discovery stage, which offers greater precision in estimating the interaction term, and the case–control approach in the replication stage to account for false positive results due to correlation of the environmental exposure with the genetic marker in the population (Piegorsch et al. 1994). There was no indication of strong associations between SNPs selected for follow-up and current use of MHT (Supplementary Figure 4), supporting the assumption of gene–environment independence. We minimized possible spurious associations due to differences in allele frequencies in the underlying populations by restriction to solely individuals of European descent. The observed genomic inflation in the case-only studies was close to one and the case–control analyses were controlled for population stratification by including genetic principal components.

In conclusion, the association between current use of MHT and risk of overall and lobular BC is potentially modified by genetic variants of genes related to mitochondrial solute carriers, and transmembrane signaling as well as immune cell activation. These findings need replication in independent studies of adequate power. The identified modest interaction effects are presently unlikely to be of clinical significance, but provide valuable insights into potential mechanisms of BC development.

Supplementary data
This is linked to the online version of the paper at http://dx.doi.org/10.1530/ERC-13-0349.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
Funding for the iCOGS infrastructure came from: the European Community’s Seventh Framework Program under grant agreement n° 223175 (HEALTH-F2-2009-223175) (COGS), Cancer Research UK (C1287/A10118, C1287/A 10710, C12292/A11174, C1281/A12014, CS047/A8384, CS047/A15007, CS047/A10692), the National Institutes of Health...
Acknowledgements

This study would not have been possible without the contributions of the following: Per Hall (COGS); Douglas F Easton, Paul Pharoah, Ykiya Michailidou, Manjeet K Bolla, Qin Wang (BCFR), Andrew Berchuck (OCAC), Rosalind A Eeles, Douglas F Easton, Ali Amin Al Olama, Zsofia Kote-Jarai, Sara Benlloch (PRACTICAL), Georgiana Chenevix-Trench, Antonis Antoniou, Lesley Mcguaffog, Fergus Couch and Ken Offit (CIMBA), Joe Dennis, Alison M Dunning, Andrew Lee, and Ed Dicks, Craig Luccarini and the staff of the Centre for Genetic Epidemiology Laboratory, Javier Benitez, Anna Gonzalez-Neira and the staff of the CNIO genotyping unit, Jacques Simard and Daniel C Tessier, Francois Bacot, Daniel Vincent, Sylvie LaBoissiere and Frederic Robidoux and the staff of the McGill University and Genome Quebec Innovation Centre, Stig E Bojesen, Sunee F Nielsen, Borge G Nordestgaard, and the staff of the Copenhagen DNA laboratory, and Julie M Cunningham, Sharon A Windebank, Christopher A Hilker, Jeffrey Meyer and the staff of Mayo Clinic Genotyping Core Facility. We thank all the individuals who took part in these studies and all the researchers, clinicians, technicians, and administrative staff who have enabled this work to be carried out. In particular, we thank: Ursula Eilber, Muhabbet Celik, Teresa Selander, Nayana Weerasooriya, Louise Brinton, Neonila Szeszenia-Dabrowska, Beata Pelpionska, Witold Zatonski, Pei Chao, Michael Stagner, The GENICA network: Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, and University of Tubingen, Germany (Wing-Yee Lo, HB); Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany (Yon-Dechun Ko, Christian Baich); Institute of Pathology, University of Bonn, Bonn, Germany (Hans-Peter Fischer); Molecular Genetics of Breast Cancer, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany (Ute Hamann); Institute for Prevention and Occupational Medicine of the German Social Accident Insurance (IPA), Bochum, Germany (TB, Beate Pesch, Sylvia Rabstein, Anne Lotz) and Institute for Occupational Medicine and Maritime Medicine, University Medical Center Hamburg-Eppendorf, Germany (VH), Heather Thorne, Eveline Niedermayer and the kConFab Clinical Follow-Up Study, the ACOs Management Group (D Bowtell, G Chenevix-Trench, A deFazio, D Gertig, A Green, P Webb), the ACS Management Group (A Green, P Parsons, N Hayward, P Webb, D Whitteman); The Australian Cancer Study Management Group (A Green, P Parsons, N Hayward, P.M Webb, and D Whitteman), project staff, collaborating institutions, clinical, and scientific collaborators and study participants.

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Printed in Great Britain

Published by Bioscientifica Ltd.


Received in final form 13 September 2013
Accepted 26 September 2013
Made available online as an Accepted Preprint 30 September 2013

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20:6 887

http://erc.endocrinology-journals.org

DOI: 10.1530/ERC-13-0349

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