Original Contribution

Pharmacogenetic Modulation of Combined Hormone Replacement Therapy by Progesterone-Metabolism Genotypes in Postmenopausal Breast Cancer Risk

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Combined hormone replacement therapy (CHRT) containing estrogens and progestins is associated with breast cancer risk. The authors evaluated interactions between CHRT use and progestin metabolism genotypes at CYP3A4 and the progesterone receptor (PGR) and their effects on breast cancer risk using the population-based Women’s Insights and Shared Experiences (WISE) Study (1999–2002) of postmenopausal Caucasian women (522 breast cancer cases, 708 controls). The authors observed an elevated risk of ductal tumors in women with 3 or more years of CHRT use and PGR 331A alleles compared with those who had neither factor (odds ratio = 3.35, 95% confidence interval (CI): 1.13, 9.99; two-sided pinteraction = 0.035). They also observed an elevated risk of progesterone receptor-positive tumors in women who had had 3 or more years of CHRT use and PGR 331A alleles compared with those who had neither factor (odds ratio = 3.82, 95% CI: 1.26, 11.55; p = 0.028). Finally, they observed an increased risk of estrogen receptor-negative tumors in women without CHRT exposure and CYP3A4*1B alleles compared with those who had neither factor (odds ratio = 6.46, 95% CI: 2.02, 20.66; p = 0.024), although the biologic interpretation of this result requires further study. When stratified by recency of use, PGR effects were observed only in current CHRT users, while CYP3A4 effects were observed only in former CHRT users. Breast cancer risk in women who have used CHRT may be influenced by genetic factors involved in progestin metabolism.

breast neoplasms; genotype; hormone replacement therapy; metabolism; pharmacogenetics; postmenopause; progesterone; risk

Abbreviations: CHRT, combined hormone replacement therapy; CI, confidence interval; ER, estrogen receptor; hPR, human progesterone receptor; HRT, hormone replacement therapy; PR, progesterone receptor.
breast cancer of 2.3 percent per year associated with HRT use. This risk appears to be increased primarily or exclusively with long-term use (13, 14). The Women’s Health Initiative (7) reported that the excess risk may be restricted to users of CHRT. Collins et al. (15) reported that use of estrogen-only replacement therapy may protect against breast cancer. While results varied by the study design used, CHRT use significantly increases breast cancer risk and may influence tumor histology and tumor marker phenotypes (16–18).

While HRT influences breast cancer risk, the excess risk conferred by CHRT may not be the same in all CHRT users. There is substantial evidence that genetic variants in candidate hormone metabolism genes may influence the disposition of exogenous hormones found in CHRT. For example, variability in hormone metabolism determined by inherited genotypes may influence breast tumorigenesis (19, 20). We hypothesize that subsets of the population may have different susceptibility to the effects of CHRT due to individual variation in genes that metabolize progestins. Both the progesterone receptor (PGR) and the cytochrome P450 (CYP3A4) genes directly or indirectly regulate progesterin metabolism and may influence whether women exposed to CHRT are differently susceptible to the breast carcinogenic effects of these compounds. The main effects of these genes on breast cancer have been previously reported (21–27), but the interaction of these genes with CHRT use has not been reported. We evaluated whether there was evidence for modification of the effect of CHRT use by genes involved in the progesterin metabolism.

MATERIALS AND METHODS

Study design and data collection

The Women’s Insights and Shared Experiences (WISE) Study is a population-based case-control study. Incident breast cancer cases were identified through hospitals and the Pennsylvania State Cancer Registry, and frequency-matched controls were identified from the community using random digit dialing. The source population for this study was from the three counties of Philadelphia (Pennsylvania), Delaware (Pennsylvania), and Camden (New Jersey). Details of the study have been reported previously (28–31).

Potentially eligible cases were Caucasian women residing in these counties at the time of diagnosis who were aged 50–79 years and newly diagnosed with breast cancer between July 1, 1999, and June 30, 2002. The cases were identified through active surveillance at 61 of 62 hospitals in these counties (one small hospital was unable to meet the regulatory requirements to obtain human subjects’ approval). The median duration from the date of diagnosis to ascertainment as eligible for inclusion in our study was 52 days and from ascertainment to interview was 226 days. Pathology reports and other medical records were reviewed to validate cancer diagnoses and to obtain information about tumor type, size, grade, stage, and hormone receptor reactivity. Breast cancer eligibility was confirmed if a pathology report was compatible with a first primary, invasive breast cancer of any stage, any grade, and any tissue type. Women with ductal carcinoma in situ, lobular carcinoma in situ, and other nonmalignant tumor types were excluded.

Controls were selected from the same geographic region as the cases and were frequency matched to the cases on age (in 5-year age groups) and calendar date of interview (within 3 months). Eligible controls had no history of breast cancer. Both cases and controls were required to live in a noninstitutional setting, to have a household telephone, to have the ability to speak English, and to have no severe cognitive, language, or speech impairment. The median duration from the screening date for random digit dialing to interview was 112 days.

We attempted to include only postmenopausal women in our study. Our definition of menopause was similar to that of the Women’s Contraceptive and Reproductive Experiences Study (32) with two modifications. Our age cutoff was 50 years to maximize the number of eligible women in the primary analysis. A sensitivity analysis using age 55 years as the cutoff for postmenopausal status in women with unknown age at menopause was performed to explore the possibility that premenopausal women between the ages of 50 and 54 years were included among those we assumed were naturally menopausal; only about 20 percent of the women with known premenopausal status were aged 55 or more years. In addition, to account for the possibility that HRT use might obscure the onset of natural menopause, we required no HRT at any time before the last menstrual period. However, we acknowledge that misclassification on menopausal status may have occurred.

Buccal swab collection, genomic DNA processing, and genotyping were undertaken as previously reported (29). The study was approved by the University of Pennsylvania Committee on Studies Involving Human Beings and by the institutional review boards of all the participating hospitals. Participants provided verbal informed consent for the interview and written informed consent for the buccal samples.

Participation

We ascertained 1,486 incident cases with breast cancer. Of these, 386 (26 percent) did not meet the age, county, pathologic, diagnosis date, and race criteria. An additional 291 were excluded from further study because they were living in a nursing home (n = 2), did not speak English (n = 17), were not mentally or physically able to participate (n = 11), did not have physician consent (n = 199), were without correct address and/or phone number (n = 43), or died before we could contact them for an interview (n = 19). Of the remaining 809, 124 (15.3 percent) refused to participate, and eight (0.9 percent) could not be interviewed before the study ended. Twenty-four cases were subsequently found during the interview to be ineligible because of medical history or age. Of the 785 cases who were eligible and accessible, 653 (83 percent) completed the interview (44 percent of those referred). Of the remaining 653 interviewed eligible cases, the 522 (80 percent) postmenopausal Caucasian women who provided a DNA biosample represent the case sample studied here.

A total of 1,337 potential controls were identified by random digit dialing. Of these, 103 (8 percent) were ineligible.
because of age, gender, county of residence, race, or medical history. Of the 1,234 remaining, 329 (27 percent) were excluded because they had physical or mental impairments (n = 11), did not speak English (n = 6), were deceased (n = 1), could not be recontacted because they had moved or changed their phone number (n = 81), or refused to participate (n = 230). Of the 905 age- and race-matched random digit dialing controls who completed the interview, four (0.4 percent) were subsequently found during the interview to be ineligible because of medical history or age. Of the 901 interviewed eligible controls, the 708 (79 percent) postmenopausal Caucasian women (53 percent of those referred) who provided a DNA biosample represent the control sample studied here.

**Statistical methods**

Odds ratio estimates and 95 percent confidence intervals were calculated to evaluate the relation between hormone metabolism genes and CHRT use with breast cancer risk. We used a lifetime exposure calendar to assess each use of all exogenous hormone use at all periods during a woman’s lifetime. This calendar asked about the first use of hormones, as well as the preparation and timing of use during that period. If there were changes to the use of hormones, or if hormone use started and then stopped, the woman was asked to report each such usage throughout her lifetime. For analysis, CHRT use was classified as never CHRT use, short-term use of CHRT (<3 years), and long-term use of CHRT (≥3 years). Although duration of CHRT use included only those periods in which a woman used CHRT, these women could have also had periods of exposure to unopposed estrogen or unopposed progestin. Those exposures were not counted in the duration of CHRT use.

Genotype coding was based on knowledge of the functional effects of the variants, as well as the frequency of the genotypes of interest (table 1). However, while we considered the biologic function of the variant, there were often insufficient data to determine genotype class. Therefore, our choice of dichotomization of genotypes for analysis was based primarily on the resulting cell frequencies that would optimize statistical power.

Multiple conditional logistic regression was used to account simultaneously for the matching variables (defined by combinations of age group and date of interview) and known risk factors for breast cancer. All models considered the same set of confounders: 1) education (less than high school, high school graduate, post-high school but not a college graduate, college graduate or higher); 2) body mass index during the age decade of the forties; 3) number of full-term pregnancies (0, 1, 2, ≥3); 4) years of menses; 5) menopause type (known natural, assumed natural at reference age of 50 years if menopausal status is unknown, and induced); 6) never/former/current smoker × years of smoking; and 7) oral contraceptive use (never, <3 years, ≥3 years). A variable was considered a confounder if it changed the point estimate of any genotype effect by 10 percent or more.

We tested for interaction between each genetic variant and CHRT use. Our a priori hypotheses of interest specified

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP, nucleotide designation (rs no.)</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Adjusted odds ratio</th>
<th>95% confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>729A</td>
<td>507</td>
<td>694</td>
<td>0.75</td>
<td>0.40, 1.38</td>
<td>0.89</td>
</tr>
<tr>
<td>PGR</td>
<td>G331A</td>
<td>507</td>
<td>694</td>
<td>0.75</td>
<td>0.40, 1.38</td>
<td>0.89</td>
</tr>
</tbody>
</table>

*Any A allele (AG/AA) vs. no A allele (GG)*

TABLE 1. Genes and alleles under study, with adjusted odds ratios for the effect of genotype, stratified by combined estrogen and progestin hormone replacement therapy use, on breast cancer risk in postmenopausal Caucasian women, Women’s Insights and Shared Experiences Study, 1999–2002

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an interaction of progesterone metabolism genotypes and CHRT use on breast cancer risk. Thus, we did not consider stratum-specific odds ratio estimates to be meaningful unless they were observed in conjunction with a statistically significant interaction effect. We undertook a 2-df test of interaction across the binary-coded genotype and three levels of CHRT (defined as never use, short-term use of <3 years, or long-term use of ≥3 years). We tested these interactions in the sample as a whole, as well as stratified by tumor histology (ductal or lobular) and estrogen receptor (ER) or progesterone receptor (PR) status (i.e., positive or negative). For comparisons stratified by tumor characteristics, the total set of 708 eligible, genotyped controls were compared with the cases in each tumor characteristics stratum. All p values are based on two-sided hypothesis tests. All analyses were performed in STATA, version 9.0, software (StataCorp LP, College Station, Texas).

RESULTS

We previously observed no statistically significant effect of CYP3A4 genotypes on breast cancer risk (31). We observed no effect of PGR on breast cancer risk (odds ratio = 1.00, 95 percent confidence interval (CI): 0.66, 1.51). Consistent with previous studies, this study demonstrated a 34 percent increase in breast cancer risk among women who had used CHRT for at least 3 years, although this effect was not statistically significant (odds ratio = 1.34, 95 percent CI: 0.97, 1.80).

In tables 1 and 2, the odds ratios refer to the effects of genotypes within each CHRT exposure group, compared with a common reference group of women who had no CHRT exposure with homozygous nonvariant genotypes. As seen in table 1, we identified no statistically significant interactions between CHRT use and any genotype in the sample as a whole. We identified statistically significant interactions between CHRT use and the studied genotypes involved in progestin metabolism, within subgroups of cases. For ductal tumors, we observed a statistically significant interaction between PGR genotype and CHRT use (p interaction = 0.035) (table 2). The adjusted odds ratio in women who had long-term CHRT exposure and who carried a PGR 331A allele was 3.35 (95 percent CI: 1.13, 9.99) compared with women who did not have CHRT exposure and carried no PGR 331A allele.

For PR-positive tumors, we observed a statistically significant interaction between PGR genotype and CHRT use (p interaction = 0.028) (table 2). The adjusted odds ratio in women with long-term CHRT use and who carried a PGR 331A allele was 3.82 (95 percent CI: 1.26, 11.55) compared with women who did not have CHRT exposure and carried no PGR 331A allele.

For ER-negative tumors, we observed a statistically significant interaction between CYP3A4*1B and CHRT use (p interaction = 0.024) (table 2). The adjusted odds ratio in

<table>
<thead>
<tr>
<th>Tumor phenotype</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>Never CHRT†</th>
<th>&lt;3 years of CHRT</th>
<th>≥3 years of CHRT</th>
<th>p interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of</td>
<td></td>
<td>Adjusted odds ratio</td>
<td>95% confidence interval</td>
<td>Adjusted odds ratio</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>Carriers of at least one CYP3A4*1B allele</td>
<td>384</td>
<td>707</td>
<td>1.75</td>
<td>0.80, 3.83</td>
<td>0.41</td>
<td>0.10, 1.57</td>
</tr>
<tr>
<td>Ductal</td>
<td>75</td>
<td>707</td>
<td>2.52</td>
<td>0.64, 9.87</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lobular</td>
<td>288</td>
<td>707</td>
<td>2.38</td>
<td>1.06, 5.33</td>
<td>0.65</td>
<td>0.16, 2.69</td>
</tr>
<tr>
<td>Progesterone receptor positive</td>
<td>144</td>
<td>707</td>
<td>3.10</td>
<td>1.11, 8.66</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Progesterone receptor negative</td>
<td>351</td>
<td>707</td>
<td>1.94</td>
<td>0.88, 4.29</td>
<td>0.48</td>
<td>0.12, 1.93</td>
</tr>
<tr>
<td>Estrogen receptor positive</td>
<td>82</td>
<td>707</td>
<td>6.46</td>
<td>2.06, 20.66</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Estrogen receptor negative</td>
<td>379</td>
<td>694</td>
<td>0.59</td>
<td>0.29, 1.22</td>
<td>0.59</td>
<td>0.29, 1.22</td>
</tr>
<tr>
<td>Ductal</td>
<td>70</td>
<td>694</td>
<td>1.83</td>
<td>0.67, 4.97</td>
<td>1.83</td>
<td>0.67, 4.97</td>
</tr>
<tr>
<td>Lobular</td>
<td>282</td>
<td>694</td>
<td>0.59</td>
<td>0.27, 1.32</td>
<td>0.59</td>
<td>0.27, 1.32</td>
</tr>
<tr>
<td>Progesterone receptor positive</td>
<td>140</td>
<td>694</td>
<td>1.58</td>
<td>0.67, 3.71</td>
<td>1.58</td>
<td>0.67, 3.71</td>
</tr>
<tr>
<td>Progesterone receptor negative</td>
<td>340</td>
<td>694</td>
<td>0.88</td>
<td>0.44, 1.74</td>
<td>0.88</td>
<td>0.44, 1.74</td>
</tr>
<tr>
<td>Estrogen receptor negative</td>
<td>82</td>
<td>694</td>
<td>1.09</td>
<td>0.33, 3.59</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* Estimated from conditional logistic regression matched on age and adjusted for age at menarche, age at menopause, number of full-term pregnancies, body mass index, and duration of oral contraceptive use.
† Compared with a common reference group of women who had no combined hormone replacement therapy exposure and did not carry the hypothesized risk “genotype class.”
‡ CHRT, combined hormone replacement therapy.
§ –, could not be estimated because of small sample size.
women who never used CHRT and who carried variant CYP3A4*1B alleles was 6.46 (95 percent CI: 2.02, 20.66) (table 2) compared with women who never had CHRT exposure and carried no CYP3A4*1B allele.

Finally, we evaluated the effects of current and former CHRT use. “Current” CHRT use included those who used CHRT within the past 6 months from the study reference date. Of the 835 CHRT users in our sample, 499 (59.8 percent) were defined as “current” users. Of the significant interactions shown in table 2, PGR genotypes interacted significantly with CHRT for ductal cancers (pinteraction = 0.032) and PR-positive tumors (pinteraction = 0.011). “Former” CHRT included those whose most recent CHRT use was at least 6 months prior to the study reference date. Of the 835 CHRT users in our sample, 336 (40.2 percent) were defined as “former” users. Of the significant interactions shown in table 2, CYP3A4 genotypes interacted significantly with CHRT for ductal cancers (pinteraction = 0.043) and ER-positive tumors (pinteraction = 0.026). These results suggest that PGR genotype effects were exerted among current CHRT users, while CYP3A4 effects were exerted among former CHRT users.

DISCUSSION

We report statistically significant interactions involving two progestin metabolism genes (CYP3A4 and PGR) and CHRT use in women with specific breast tumor characteristics. Progesterone exposure in relation to the menstrual cycle and pregnancy is associated with protection from breast cancer (33), but progestin-only contraceptives have not been associated with increased breast cancer risk (34). Synthetic progestins found in CHRT are associated with increased breast cancer risk (15). In the United States, the primary synthetic progestin in CHRT is medroxyprogesterone acetate, a progestin with estrogenic, androgenic, and hepatocellular effects (35–37) that are not properties of endogenous progesterone and may be responsible for the carcinogenic effects of CHRT.

We identified interactions between PGR genotypes and CHRT in ductal and PR-positive tumors and between CYP3A4 and CHRT in ER-negative tumors. Women who have long-term CHRT use are at increased risk of ductal or PR-positive tumors if they have inherited the PGR 331A variant. These results are consistent with the hypothesized function of the PGR 331A allele. The human progestosterone receptor (hPR) has two distinct isoforms (hPR-A and hPR-B) encoded from a single gene (PGR) by transcription at two distinct promoters and by translation initiation from two alternative translation start sites (38). The 331A allele increases transcription of hPR-B relative to hPR-A (39). The hPR-B isoform is associated with transcriptional activation, while the hPR-A isoform is transcriptionally inactive and represses the activity of hPR-B (40). Therefore, carriage of the 331A allele (i.e., hPR-B) is associated with an active progesterone-responsive promoter that would be hypothesized to promote breast cell proliferation. This hypothesis is supported by a mouse model in which the B isoform is associated with epithelial cell proliferation and that relative expression of the A and B isoforms is an important determinant of the effectiveness of progestin therapy (41). We did not observe a significant main effect of PGR genotypes with breast cancer, which is consistent with some reports (23, 25), but not others (22, 24).

It has been suggested that CHRT use is associated with an increased risk of lobular breast tumors (17, 18), but studies have not evaluated whether this effect is modulated by genotypes involved in CHRT metabolism. Unfortunately, the present study appears to have had insufficient power to detect associations for lobular tumors or to formally test the three-way interaction among genotype, CHRT exposure, and tumor type (table 2). We also report that there were significant interactions of CHRT use with CYP3A4 genotypes in ER-negative tumors. The CYP3A4 enzyme is known to metabolize both estrogen and progestins to hydroxylated forms. We hypothesize that the hydroxylation of progestins found in CHRT may influence the effect of CHRT on breast cancer risk. CYP3A4*1B is an A→G nucleotide change at position −290 (denoted A−290G) in the nifedipine-specific element in the 5′-regulatory region of CYP3A4. CYP3A4*1B has been associated epidemiologically with a variety of traits and diseases (42–47), but not with breast cancer risk (21, 27). The literature has not consistently supported the hypothesis that CYP3A4*1B has a functionally significant effect on the expression or activity of CYP3A4. Hashimoto et al. (48) identified several regulatory elements, including the nifedipine-specific element that contains the CYP3A4*1B variant. Lamba et al. (49) reported that CYP3A4*1B alleles were found significantly more frequently in Caucasians with low CYP3A4 protein levels than in those with higher levels. A number of authors (27, 49–53) have studied the relation of CYP3A4 expression or function with the CYP3A4*1B promoter without achieving consensus about the biologic meaningfulness of this variant. However, most studies have reported consistently elevated expression associated with CYP3A4*1B (a 20–200 percent increase) over the consensus CYP3A4*1A (54). Whether this magnitude of phenotypic change is sufficient to influence breast cancer risk under CHRT exposure is not clear. However, the direction of effects reported here suggests that the increased metabolism of progestins by CYP3A4*1B leads to protection from breast cancer, while increases in 16α-, 2β-, or 6β-hydroxyprogesterone formation by CYP3A4 may increase risk among women who are not exposed to CHRT. The relative contribution of progestin metabolism versus formation of catecholestrogens by CYP3A4 in breast carcinogenesis cannot be fully explained by the present data. Furthermore, the sample size available to test for interactions between CHRT and CYP3A4*1B was limited in this study. Therefore, although we have identified statistically significant effects, it is critical to confirm these results using larger sample sizes.

Despite the strength and biologic plausibility of most of the associations reported here, there are limitations to the present study. As described above, we have chosen putative functional variants for study here. However, we cannot be sure that the associations identified here are themselves the “causative” genotype events, or if they are in linkage disequilibrium with other alleles in the same or different genes that are causative of the effects reported here. In particular,
CYP3A4 is part of a multigene family with strong linkage disequilibrium blocks (55), so it is possible that one or more other members of the CYP3A multigene family could be responsible for the effects observed here. We have restricted our inferences to Caucasians, in order to limit the potential for confounding by ethnicity (population stratification). Most authors now agree that the potential for bias due to population stratification in populations of European descent is minimal (56–58). Although we collected data on African-American women, the sample size was insufficient to identify relevant interactions, and we have not presented those data here. Although we have limited our analyses to evaluate first-order interactions between genotypes and CHRT use, the sample sizes required to test for interaction between these factors became very small in some situations. Therefore, we may have missed some important effects in cases in which the genotype-CHRT groups were small. We have also limited ourselves a priori only to situations in which significant interactions between genotype and CHRT were identified and did not consider individual (stratum-specific) odds ratios as having a particular interpretation unless a statistically significant interaction was present. There is also potential for misclassification on CHRT use. We used a very detailed lifetime exposure calendar to assess all periods of HRT use of all types. This assessment included “show cards” with pictures of HRT pills, patches, creams, and other preparations to remind women of their possible HRT uses. However, recalled exposure assessments are inherently limited, and misclassification of exposure, including differential recall biases between cases and controls, may have influenced our results. We have undertaken a separate validation of reporting of exposure assessment among the women in this study (59), which suggested that recall of HRT use was reasonably good but improved if drug names and show cards were used as reminders during the interview.

Finally, we tested 42 primary hypotheses regarding interactions between genotypes and CHRT use (tables 1 and 2). Many other hypothesis tests could be considered when evaluating the potentially large number of interactions between genotype and various CHRT groupings, so by limiting our hypotheses, we may have missed some important effects, but we also limited the potential for false positive results. As suggested by Wacholder et al. (60), we calculated the false positive report probability to evaluate whether any of the effects reported here may represent “noteworthy” results. The false positive report probability was less than 0.2 for prior probabilities of 10–20 percent. Although no clear criteria exist for the appropriate prior probability level to consider, because we have studied genes and exposures with a strong a priori evidence of association and numerous previous publications addressing the main effect of these factors, this prior probability level may be appropriate. Therefore, these odds ratios can be considered noteworthy (i.e., unlikely to represent false positive reports) on the basis of the criteria of Wacholder et al. (60).

In summary, we report novel observations that breast cancer risk associated with CHRT use may be influenced by functionally relevant variants in CYP3A4 or PGR, both of which are known to metabolize progestins. These results suggest that breast cancer risk in women who use CHRT may depend on genetic factors involved in progestin metabolism. These data have potential clinical implications for breast cancer risk in women who have used CHRT. CHRT is associated with increased breast cancer risk (15). If confirmed, interaction of the PGR or CYP3A4 genotype and CHRT use may identify women who may be particularly susceptible to breast cancer if exposed to CHRT. For example, women who carry a variant genotype that increases their breast cancer risk and have had CHRT exposure may require increased breast surveillance or be good candidates for other preventive strategies compared with women who have used CHRT but do not carry these genotypes.

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Conflict of interest: none declared.

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