Confirmation of the reduction of hormone replacement therapy-related breast cancer risk for carriers of the *HSD17B1*_937_G variant

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Abstract

17β-hydroxysteroid dehydrogenase type 1 (HSD17B1) plays an important role in the biosynthesis of 17β-estradiol. The current study aimed at confirming the reduced risk of breast cancer in carriers of the non-synonymous *HSD17B1*_937_A>G (rs605059) polymorphism who used any hormone replacement therapy (HRT) for ten years or longer. We performed an independent association study using four breast cancer case-control studies from Australia, Germany and Sweden. In all, 5,777 cases and 8,189 age-matched controls of European descent were genotyped by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and TaqMan. Risk estimates were calculated by interaction analysis and main effect analysis adjusted for age and study. Main effect analyses for women using any HRT for 10 years or longer (1,428 cases versus 1,724 controls) revealed a protective effect of the *HSD17B1*_937_G allele on breast cancer risk (OR 0.86, 95% CI: 0.73-0.99; p = 0.048). Thus, our previous finding of a protective effect of the *HSD17B1*_937_G allele on HRT-associated breast cancer risk has now been confirmed both in independent large patient cohorts and a comprehensive pooled analysis supporting the hypothesis, that a HSD17B1-mediated decreased conversion of estrone to the more potent 17β-estradiol may reduce the estrogenic effects, thereby reducing the risk of developing breast cancer during long-term HRT use.

Introduction

The 17β-hydroxysteroid dehydrogenase type 1 (HSD17B1) is a key enzyme in the sex steroid hormone metabolism pathway that mediates the catalytic conversion of less active estrone to its most potent form, 17β-estradiol [1]. Since elevated steroid hormone levels can result from variations in genes encoding enzymes of the steroid metabolism pathway, such genetic variations have been suggested to contribute to an increased breast cancer risk especially in postmenopausal women [2]. Notably, HSD17B1, a member of this pathway, is predominantly expressed in steroidogenic tissues and its over-expression has been observed in estrogen-sensitive cancers. Moreover, increased HSD17B1 activity has been observed in breast tumors of postmenopausal but not premenopausal women [3-5]. Interestingly, *HSD17B1* polymorphisms have not been prioritized among the over 20 novel breast cancer susceptibility genes reported from genome-wide association studies (GWAS) conducted with large global case-control collections [6-8]. Despite a lack of evidence but due to the HSD17B1 involvement in steroid metabolism, its polymorphisms may likely contribute to breast cancer risk, however there is a possibility that this may become only evident for the risk associated with hormone replacement therapy (HRT). HRT is commonly prescribed as estrogen plus progestin or estrogen monotherapy for the relief from menopausal symptoms such as hot flushes and has been commonly accepted as a breast cancer risk factor particularly when used for more than 5 years [9, 10]. The number of studies that have previously examined the relevance of *HSD17B1* polymorphisms and HRT use are rather limited and provide inconsistent results [3, 11-15]. Our follow-up investigation of whether or not a genetic *HSD17B1* polymorphism contributes to an HRT-associated breast cancer risk is based on a German molecular epidemiology study MARIE-GENICA [16] which suggested a reduced breast cancer risk for female carriers of the *HSD17B1*_937_G allele having used any long-term HRT.

The non-synonymous polymorphism rs605059 at nucleotide position 937 of the *HSD17B1* gene is located at chromosome 17q12 with a minor allele frequency of 48% in Europeans [17]. The polymorphism causes an amino acid exchange from Serine to Glycine at position 313 in exon 6 [3, 15] and the absence of other frequent non-synonymous polymorphisms within the *HSD17B1* coding region made this the polymorphism of interest. Following the hypothesis that genetic risk modifiers could aid in the stratification of patients into those with and without a confounding risk for breast cancer in HRT users, and based on the previous finding of an *HSD17B1*_937_G association with HRT-related breast cancer risk, we set out to validate this association using two independent breast cancer case-control collections with available HRT information (any HRT use) from Sweden (SASBAC) and Australia (MCCS). Here we report the confirmation of the reduced risk effect of the *HSD17B1*_937_G allele in the context of long-term HRT use both in the independent studies and in the pooled analysis including the MARIE-GENICA study.

Materials and methods

Study populations

The study sample included 5,777 breast cancer cases and 8,189 controls from four studies from Australia, Germany and Sweden. All women were of European descent. The Australian prospective Melbourne Collaborative Cohort Study (MCCS) is a prospective study including 41,514 residents of the city of Melbourne (24,469 women) aged between 40 and 69 years at base-line out of which 677 breast cancer cases diagnosed during follow-up and 778 controls were randomly selected [18]. The population-based Singapore and Swedish Breast Cancer Study

(SASBAC) comprised 3,345 breast cancer cases and 3,454 age-matched controls from Sweden, aged between 50 and 74 years [19]. For a pooled analysis, data from the previously published MARIE-GENICA study on these subjects were included [16]. The latter is a joint investigation of two population-based German breast cancer case-control studies: MARIE (MAmmakarzinom RIsikofaktor Erhebung) [20] and GENICA (Gene ENvironment Interaction and Breast CAncer in Germany) [21, 22] which together included 3,149 breast cancer patients with primary breast cancer and 5,489 age-matched controls. Participants were aged between 50 and 80 years. All studies were approved by respective ethical review committees and participants gave written informed consent.

Data on any HRT use were available for 4,912 patients and 7,137 controls, of which 1,428 cases and 1,724 controls used HRT for 10 or more years.

Genotyping and statistical analysis

Genotyping of blood-derived DNA from SASBAC participants was done using Sequenom® Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Sequenom, San Diego, CA, USA) as previously done for the MARIE-GENICA participants [16]. Genotyping of blood-derived DNA from MCCS participants was done by TaqMan® analysis using the Genotyping Assay, Human SM, C___2350902_10 (Applied Biosystems, Foster City, CA, USA).

Statistical analysis was done by logistic regression with adjustment for study and age: a) main effect analysis of *HSD17B1*_937 A>G and use of HRT for 10 years or longer. (Pooled: 1,411 cases and 1,715 controls successfully genotyped); b) interaction analysis between *HSD17B1*_937

A>G and duration of HRT use (Pooled: 4,824 cases and 7,041 controls successfully genotyped). Risk estimates are given as odd ratios (OR) along with 95% confidence interval (CI). The validation study had an 80% power to detect a minimum OR of 0.84 for the main effect analysis of the *HSD17B1* polymorphism under investigation ($\alpha = 0.05$, two-sided test). Analysis for a potential association between genotype and respective tumor steroid hormone receptor status was done also for ER-positive cases versus ER-negative cases and PR-positive cases versus PR-negative cases. All statistical analyses were performed using the freely available R-package R-2.11.1 (SNPassoc-1.8-5) (www.r-project.org) and SPSS v. 15.0 (SPSS Inc., IBM Corporation, NY, USA), respectively. Statistical significance was defined as $p < 0.05$.

Results

*HSD17B1*_937_A>G genotype frequencies of cases and controls met Hardy-Weinberg equilibrium. Call rates were greater than 98% and repeated analyses of the duplicate samples (10%) showed 100% concordance. After adjusting for potential confounders (age and study), we observed no statistically significant association between any of the *HSD17B1*_937_A>G genotypes and overall or hormone receptor-dependent breast cancer risk (data not shown). In the previous MARIE-GENICA study, interaction analysis showed a reduced breast cancer risk for women carrying the homozygous *HSD17B1*_937_GG genotype with long-term HRT use ($p_{\text{interaction}} = 0.032$, Table 1). This effect was not seen in the interaction analysis of the MCCS and SASBAC collections (data not shown).

To compare the effects of each genotype on an HRT associated breast cancer risk we performed a main effect analysis of the subgroup of long-term HRT users (10 years or longer). Within the MCCS and SASBAC studies, we observed a protective effect for carriers of the GG genotype

with an OR of 0.56 (95% CI: 0.32-0.96; p = 0.041; Table 1). When we looked at women with HRT use 10 years and longer, the main effect analysis of the MARIE-GENICA study did not show a significant protective effect (Table 1). The pooled main effect analysis of the MCCS, SASBAC, MARIE-GENICA confirmed the significant decreased breast cancer risk for carriers of the *HSD17B1*_937_G variant (OR 0.86, 95% CI 0.73-0.99; p = 0.048; Table 1).

Discussion

Our pooled analysis of four international breast cancer case-control studies with available data on any HRT use confirmed the protective effect of the *HSD17B1*_937_G allele on breast cancer risk in women using HRT for 10 years or longer. Although the functional effect of the non-synonymous *HSD17B1*_937_A>G polymorphism is largely unknown, it has been suggested that the variant G allele may lead to decreased enzyme activity *in vitro* [3, 15]. Accordingly, the observed decreased risk effect is in line with the current knowledge of the role of HSD17B1 in the biosynthesis of 17β-estradiol [1] whereby lower activity of the G variant may lead to decreased estrogenic effects on breast epithelial tissue during HRT use, thus lowering the risk of developing breast cancer.

In a previous study of the MARIE-GENICA breast cancer case-control collection, we observed an interaction between the *HSD17B1*_937_GG genotype and reduced breast cancer risk with duration of HRT [16]. This statistical modeling provided us with information on the effect of a genotype on the breast cancer risk effect across all categories of duration of HRT use. Although this interaction study suggested a link between the *HSD17B1* G allele and HRT-related breast

cancer risk, it limits the direct comparison between patients with different genotypes. For that reason, in the current investigation, we put emphasis on a main effect analysis to directly compare the risk effect of the different *HSD17B1*_937 genotype groups, i.e. AA versus AG, AA versus GG and AA versus AG+GG. This statistical modeling is commonly used in pharmacogenetic studies for risk stratification [23]. Of note, the main effect analysis also enabled us to specifically examine the subgroup of long-term HRT users (10 years or longer) without bias from HRT users with shorter duration. Notably, large clinical and epidemiological studies have shown the HRT-related breast cancer risk for only long-term use [9, 10]. Therefore, our findings are important and provide a clue to better understand possible underlying mechanisms involved in HRT-related breast cancer risk.

The analysis of two independent study collections, MCCS and SASBAC, validated our hypothesis of a protective effect of the *HSD17B1*_937_GG genotype derived from the initial MARIE-GENICA study. The pooled analysis including all breast cancer case-control collections MARIE-GENICA, MCCS and SASBAC confirmed this decrease in risk and moreover, suggests a co-dominant effect, in that carriers of the *HSD17B1*_937_G variant have a decreased breast cancer risk with long-term HRT use.

The strength of our study is the confirmation of the hypothesis of a reduced breast cancer risk effect for carriers of the G variant of the *HSD17B1*_937_A>G polymorphism in association with long-term HRT use in independent, large, and age-matched pooled study collections. The study size allowed for a well powered analysis. Although the main effect is not statistically significant in MARIE-GENICA, the direction of the effect is in line with the MCCS and SASBAC results. We suggest that the effect of this genetic variant is reproducible but small.

In conclusion, women who are carriers of the *HSD17B1*_937_G variant and use any HRT for 10 years or longer are more likely to be diagnosed with breast cancer than non-carriers. The *HSD17B1*_937_G variant does not influence breast cancer risk in women not using HRT. This genetic predisposition should encourage further association studies towards a better understanding of the inter-individual differences in the HRT-related breast cancer risk eventually leading to safer HRT use in the future.

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Conflict of interest

The authors have no conflict of interest.

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Table 1 Association between *HSD17B1*_937_A>G genotypes and hormone replacement therapy-related breast cancer risk

Study	*HSD17B1* Genotypes	Cases *n* (%)	Controls *n* (%)	OR (95% CI)	*p* value
Interaction Analysis					
Initial study					
MARIE-GENICA [1]	AA	916 (29.4)	1,613 (29.8)	1.17[a] (1.10-1.25)	
	AG	1,592 (51.0)	2,702 (49.9)	1.10[a] (1.05-1.16)	
	GG	610 (19.6)	1,102 (20.3)	1.11[a] (1.02-1.20)	0.032
Main Effect Analysis (subgroup of HRT users for 10 years or longer)					
MARIE-GENICA	AA	359 (30.3)	444 (27.7)	1.00[b]	
	AG	591 (49.8)	833 (52.0)	0.88[c] (0.74-1.05)	0.141
	GG	236 (19.9)	324 (20.2)	0.95[c] (0.85-1.06)	0.339
	AG+GG	827	1,157	0.88[c] (0.75-1.04)	0.142
Validation study MCCS and SASBAC	AA	84 (37.3)	44 (38.6)	1.00[b]	
	AG	108 (48.0)	50 (43.9)	0.86[c] (0.35-2.11)	0.741
	GG	33 (14.7)	20 (17.5)	0.56[c] (0.32-0.96)	0.041
	AG+GG	141	70	0.64[c] (0.28-1.47)	0.294
Pooled Analysis MCCS, SASBAC and MARIE-GENICA	AA	443 (31.4)	488 (28.5)	1.00[b]	
	AG	699 (49.5)	883 (51.5)	0.86[c] (0.73-1.01)	0.065
	GG	269 (19.1)	344 (20.1)	0.92[c] (0.83-1.02)	0.124
	AG+GG	968	1,227	0.86[c] (0.73-0.99)	0.048

[a]Models stratified by study region and year of birth in five year classes (≤1934, 1935-1939, 1940-1944, 1945-1949, ≥1950) and adjusted for type of menopause natural, bilateral oophorectomy or radiation or chemotherapy, hysterectomy, unknown, other), number of births (0,1,2,3,4+), breastfeeding (never, ever), smoking (never, ever), number of mammograms (0,1-4, 5-9, ≥10, missing), benign breast disease (never, ever), family history of breast cancer in first degree relative (yes, no), BMI (≤22.4, 22.5-24.9, 25.0-29.9, ≥30 kg/m^2)

[b]Reference

[c]OR adjusted for age and study

CI confidence interval; *HSD17B1* 17β-hydroxysteroid dehydrogenase type 1; *OR* odds ratio

Reference

1. MARIE GENICA (2010) Postmenopausal estrogen monotherapy-associated breast cancer risk is modified by *CYP17A1*_-34_T>C polymorphism. BCRT 120:737-744

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