CYP17 genotype is associated with short menstrual cycles, early oral contraceptive use and BRCA mutation status in young healthy women

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The CYP17 gene is involved in steroid hormone metabolism and has been proposed as a low penetrance gene for breast cancer. We aimed to investigate the associations between the CYP17 genotype and breast cancer risk factors, such as age at menarche, menstrual cycle length, oral contraceptive (OC) use, and BRCA mutation status among 258 healthy young women, aged ≤40, from 158 breast cancer high-risk families. Questionnaires including questions on reproductive factors and OC use were completed and blood samples were obtained from all women. CYP17 (rs743572) was genotyped with sequencing in 254 women. The main findings were that short menstrual cycles (<27 days) were significantly more common with increasing number of variant A2 alleles (8%, 17% and 32%; P\text{trend} = 0.002, adjusted for family clustering). Each A2 allele was associated with a 7 months earlier OC start (17.8, 17.0, and 16.6 years; P\text{trend} = 0.014, adjusted for age at menarche, ever-smoking and family clustering). Homozygosity for the A2 allele was more common among known non-carriers from BRCA1/2 families compared with other high-risk women OR 2.92 (95% CI 1.49–5.73; P = 0.002, adjusted for family clustering). We found no association between CYP17 genotype and age at menarche. In conclusion, this study suggests that short menstrual cycles, age at first OC use and BRCA mutation status may need to be considered in studies exploring the relationships between CYP17 and risk factors for early onset breast cancer.

Key words: BRCA1/2; breast cancer; menstrual cycle length; CYP17 polymorphism; oral contraceptives

Introduction

Breast cancer is the most common form of cancer among women in Western societies; the lifetime risk is 1 in 10 in Sweden (data from the Swedish National Cancer Registry), 1 in 12 in the UK (Pharoah and Mackay, 1998) and 1 in 8 in the USA (National Cancer Institute, 1999). Risk factors include both genetic factors and non-genetic factors such as age at menarche, menstrual cycle length, hormone levels, exogenous hormone exposure and a family history of the disease (Key et al., 2001). Disease causing mutations in the BRCA1 and BRCA2 genes confer a substantially increased risk of developing breast cancer and ovarian cancer at a young age (McPherson et al., 2000; Narod and Foulkes, 2004; Lacroix and Leclercq, 2005). However, a significant proportion of the breast cancer families with a dominant pattern of inheritance are non-BRCA1/2 families, also referred to as BRCAX families. Their pathogenesis is believed to depend on polymorphisms in several low penetrance and high prevalence genes working in combination with environmental factors (Narod and Foulkes, 2004; Lacroix and Leclercq, 2005). The CYP17 gene may be such a low penetrance gene (Feigelson et al., 1997; Bergman-Jungeström et al., 1999).

The CYP17 gene encodes the enzyme cytochrome P450c17α enzyme, which catalyses both 17α-hydroxylation and 17,20-lyase conversion of 21-carbon steroids to 17-carbon precursors of sex steroids. It contains a T to C polymorphism in the 5′ promoter region that results in the A1 and A2 alleles, respectively. The A2 allele is thought to increase the transcriptional activity of the CYP17 gene leading to increased levels of estrogen (Feigelson et al., 1998; Haiman et al., 1999; Onland-Moret et al., 2005) which may increase the risk of breast cancer (Henderson and Feigelson, 2000). Many genes influence steroid hormone biosynthesis and metabolism, and polymorphisms in these genes may explain some of the inter-individual differences in hormone levels and breast cancer risk (Mitrunen and Hirvonen, 2003). Feigelson et al. (1997) and Bergman-Jungeström et al. (1999) reported that the CYP17 genotype affects breast cancer risk. Subsequent studies have shown conflicting results (Dunning et al., 1998; Feigelson et al., 1998; Haiman et al., 1999; Mitrunen et al., 2000; Yager, 2000; Garcia-Closas et al., 2002; Ye and Parry, 2002; Travis et al., 2004; Chang et al., 2005; Einarsdottir et al., 2005; Small et al., 2005; Verla-Tebit et al., 2005). These conflicting results might be due to the fact that other known breast cancer risk factors were not fully taken into account.

Early menarche is an established risk factor for early onset breast cancer (Henderson and Feigelson, 2000). Luri et al. (2005) reported that CYP17 A2 allele carriers had a significantly younger age at menarche, whereas Small et al. (2005) found no such association. A short menstrual cycle is also associated with an increased risk of breast cancer (Olsson et al., 1983; Kelsey et al., 1993; Whelan et al., 1994), especially prior to age 40 years (Terry et al., 2005).
A recent small study showed that the A2 allele was significantly more common in women with a short menstrual cycle (<27 days) (Small et al., 2005) and suggested that CYP17 may be a marker for endocrine function.

Combined oral contraceptive (OC) pills may also modify the risk of developing early onset breast cancer, especially in women who began to use OCs prior to age 20 years (Olsson et al., 1989; Velentgas and Daling, 1994; Collaborative Group on Hormonal Factors in Breast Cancer 1996; Henderson and Feigelson, 2000; Key et al., 2001; Kumle et al., 2002; Mitrunen and Hirvonen, 2003; Jernström et al., 2005). At least two studies have reported that women homozygous for the A2 allele were less likely to have ever used OCs or hormone replacement therapy (HRT) (Feigelson et al., 1998; Onland-Moret et al., 2005). Conversely, Ambrosone et al. (2003) reported no relationship between CYP17 genotype and use of OC. To our knowledge, there are no studies exploring whether the CYP17 genotype is linked to OC start age.

A family history of breast cancer is known to approximately double the risk of breast cancer (Pharoah et al., 1997). Spurde et al. (2000) reported an excess of homozygous CYP17 A2 allele carriers among breast cancer patients diagnosed before age 40 years with a family history, after exclusion of known BRCA1 and BRCA2 mutation carriers. This study was then expanded to include older cases (Cui et al., 2003) and the authors reported that the best fit for a statistical model for the relationship between CYP17 and breast cancer was a recessive model excluding BRCA1 and BRCA2 carriers. Crude analysis of the data from a German study (Verla-Tebit and Chang-Claude, 2000) suggests that homozygosity for the A2 allele is inversely associated with risk for premenopausal breast cancer in women with a family history of the disease in first-degree relatives. In Sweden, ~9% of women diagnosed with breast cancer at age 40 years or younger carry a BRCA1 or BRCA2 mutation (Loman et al., 2001). BRCA1 mutations are more common than BRCA2 mutations (Loman et al., 2001). To our knowledge, there are no studies investigating whether the CYP17 A2 allele is associated with BRCA mutation status in high-risk breast cancer families.

The aim of this study was to further investigate the associations between the CYP17 genotype and breast cancer risk factors such as age at menarche, menstrual cycle length, patterns of OC use and BRCA mutation status in a cohort of young healthy women from breast cancer high-risk families.

Materials and methods

Study population
Two hundred and fifty-four women consented to genotyping of the CYP17 gene. Genomic DNA was extracted from 300 μl of peripheral blood using Wizard, Genomic DNA Purification Kit, Promega. PCR primers 5'-CA AAAGTCGAGGCTGAAGATCAG and 5'-TTGGTGAGGCAAGCAAGA yielded a 150bp nucleotide sequence. A single-base pair polymorphism in the untranslated 5' region, CCACT/C, was screened (rs743572). PCR was performed in 25 μl reactions using 25 ng of DNA, 0.2 μM of each primer, 0.1 mM of each deoxynucleotide (Amersham Biosciences, Buckinghamshire, UK), 2.5 mM MgCl2 (Applied Biosystems, Foster City, CA, USA), 1 × PCR Gold Buffer (Applied Biosystems, Foster City, CA, USA) and 0.5 U AmpliTaq Gold (Applied Biosystems, Foster City, CA, USA). The PCR product was sequenced (Big Dye, Terminator Cycle Sequencing, Applied Biosystems, Foster City, CA, USA) according to the manufacturer’s instructions and run on an ABI 3100 Genetic Analyser. We re-analysed 47 samples for quality control. Out of the 47 samples, 43 worked at the first attempt. The concordance rate was 100% when compared with the original results. We did not re-analyse the remaining four samples.

CYP17 genotyping
Two hundred and fifty-four women consented to genotyping of the CYP17 gene. The statistical software SPSS 11.0.2 and Stata 9.2 were used for all statistical analyses. Student’s t-test was used to compare continuous variables, such as age at menarche and body sizes between the different CYP17 genotypes. Chi-square was used to compare the frequency of dichotomous variables such as ever smoking and percentage of OC users in relation to CYP17 genotypes (A1/A1, A1/A2 and A2/A2) as well as the A1 and A2 allele frequencies between the different groups of BRCA4 mutation status. The unofficial Stata routine genhwi (Clevves, 1999) was used to test whether the CYP17 A1 and A2 alleles were in Hardy–Weinberg equilibrium. The relationship between CYP17 genotype and age at first OC use was also examined in a multivariate linear regression model, adjusting for other variables. The multivariate linear analyses on the relationship between the CYP17 genotype and OC start age as well as CYP17 genotype and short menstrual cycles were also re-run with further adjustment for family clustering using the cluster option of the regress command in Stata. The odds of being a homozygous A2 allele carrier in relation to BRCA2 mutation status was examined in a chi-square model. This analysis was also re-run with further adjustment for family clustering using the cluster option of the logistic command in Stata. A P-value of <0.05 was taken to be significant. All P-values were two-sided.
Results

The baseline characteristics of the 258 women stratified by CYP17 genotype are presented in Table I. Eighty women had the A1/A1 genotype, 138 women had the A1/A2 genotype and 36 women had the A2/A2 genotype. The allele frequency distribution did not significantly deviate from the Hardy–Weinberg equilibrium (P = 0.06).

The only reproductive factors in Table I that differed between the CYP17 genotypes were OC use start age and frequency of short menstrual cycles, defined as <27 days according to Small et al. (2005). Each CYP17 A2 allele was associated with a 7 month earlier age at first OC use (P trend = 0.02). Other factors associated with an early OC use start age were age at menarche and ever smoking. These two factors were not associated with the CYP17 genotype. Women with an age of menarche prior to age 13 years started using OCs on average 14 months earlier (P = 0.001) than women with an age of menarche of 13 years or older. Being an ever smoker was associated with a 20 month earlier age at first OC use. In a multivariate model (n = 229) including these three factors, an early age at first OC use was significantly associated with an increasing number of A2 alleles (P trend = 0.014), being an ever smoker (P trend < 0.001) and age at menarche prior to age 13 (P trend = 0.003), adjusted for family clustering. Further adjustment for time to regular menses were established (6 months or longer, yes/no), did not materially change the relationship between the number of A2 alleles and a younger age at first OC use, but several women had missing information on this variable (n = 68). There were no other differences in reproductive factors, duration of OC use, body size, or smoking habits in relation to the CYP17 genotype.

Although the mean menstrual cycle length did not differ between the CYP17 genotypes, we found that a short menstrual cycle (<27 days) was significantly more common among women homozygous for the A2 allele. The distribution of a menstrual cycle shorter than 27 days was 8% in the A1/A1 group, 17% in the A1/A2 group and 32% in the A2/A2 carrier group (P trend = 0.002, adjusted for family clustering).

CYP17 and menstrual cycle length

The CYP17 A2 allele was not distributed equally among the women with various BRCA mutation status. The CYP17 allele distribution was in Hardy–Weinberg equilibrium among BRCA1/2 non-carriers (P = 0.22), among BRCA1 carriers (P = 0.25), among BRCA2 carriers (P = 0.29) and among untested women (P = 0.30), but not among women from BRCAX families (P = 0.01). The odds of being a homozygous A2 allele carrier was approximately three times higher in women who had tested negative for the respective mutation in their family, i.e. BRCA1/2 non-carriers, compared with the remaining high-risk women OR 2.92 (95% CI 1.49–5.73; P = 0.002), adjusted for family clustering. This was also true for each of the high-risk groups BRCA1/2 carriers, BRCAX family and untested women, Table II. The number of mutation carriers was low, therefore, we tested an additional 77 female BRCA1/2 mutation carriers who were not part of the original study. These women had available DNA for CYP17 genotyping, came from the same health-care region, were born in 1956 or later and 35 had been diagnosed with breast or ovarian cancer at the time of mutation testing. The results remained essentially the same but became significant also for the BRCA1/2 mutation carriers; i.e. it was significantly more common to carry the CYP17 A2/A2 genotype among non-carriers than among BRCA1/2 carriers OR 3.13 (95% CI 1.41–7.14; P = 0.005), adjusted for family clustering (Table II).

Discussion

The main findings of this study were that women homozygous for the A2 allele had a significantly higher proportion of short menstrual cycles (<27 days), that the CYP17 A2 allele was associated with an earlier start age of OC use and that homozygosity for the CYP17 A2 allele was approximately three times more common among non-carriers than among BRCA1/2 carriers OR 3.13 (95% CI 1.41–7.14; P = 0.005), adjusted for family clustering (Table II).

Table I. Characteristics of women in the study

<table>
<thead>
<tr>
<th></th>
<th>All women</th>
<th>CYP17 (A1/A1)</th>
<th>CYP17 (A1/A2)</th>
<th>CYP17 (A2/A2)</th>
<th>P trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 258)</td>
<td>(n = 80)</td>
<td>(n = 138)</td>
<td>(n = 36)</td>
<td></td>
</tr>
<tr>
<td>Year of birth</td>
<td>1970 (± 7.0)</td>
<td>1969 (± 6.7)</td>
<td>1970 (± 6.7)</td>
<td>1969 (± 8.2)</td>
<td>0.99</td>
</tr>
<tr>
<td>Age at baseline, years</td>
<td>29.2 (± 6.4)</td>
<td>30.1 (± 6.4)</td>
<td>28.6 (± 6.0)</td>
<td>29.8 (± 7.3)</td>
<td>0.46</td>
</tr>
<tr>
<td>Age at menarche, years</td>
<td>12.8 (± 1.3)</td>
<td>12.8 (± 1.4)</td>
<td>12.8 (± 1.2)</td>
<td>12.8 (± 1.3)</td>
<td>0.77</td>
</tr>
<tr>
<td>Menstrual cycle length, days</td>
<td>28.3 (± 3.3)</td>
<td>28.6 (± 4.6)</td>
<td>28.2 (± 2.2)</td>
<td>27.6 (± 3.0)</td>
<td>0.21</td>
</tr>
<tr>
<td>Short menstrual cycles, &lt;27 days, %</td>
<td>16</td>
<td>8</td>
<td>17</td>
<td>32</td>
<td>0.003</td>
</tr>
<tr>
<td>Time to regular cycles, ≤6 months, %</td>
<td>62</td>
<td>66</td>
<td>57</td>
<td>69</td>
<td>0.91</td>
</tr>
<tr>
<td>Parous at baseline, %</td>
<td>49</td>
<td>52</td>
<td>46</td>
<td>53</td>
<td>0.95</td>
</tr>
<tr>
<td>Age at first birth in parous women</td>
<td>24.8 (± 4.0)</td>
<td>25.4 (± 3.8)</td>
<td>24.3 (± 3.7)</td>
<td>24.6 (± 4.8)</td>
<td>0.33</td>
</tr>
<tr>
<td>Ever smoker, %</td>
<td>42</td>
<td>39</td>
<td>43</td>
<td>44</td>
<td>0.50</td>
</tr>
<tr>
<td>Oral contraceptives, ever %</td>
<td>92</td>
<td>93</td>
<td>92</td>
<td>92</td>
<td>0.87</td>
</tr>
<tr>
<td>Start age, years</td>
<td>17.2 (± 2.7)</td>
<td>17.8 (± 2.9)</td>
<td>17.0 (± 2.6)</td>
<td>16.6 (± 2.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>OC total duration, months</td>
<td>79.9 (± 57.1)</td>
<td>79.3 (± 59.0)</td>
<td>80.8 (± 54.8)</td>
<td>80.3 (± 63.4)</td>
<td>0.95</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168 (± 5.9)</td>
<td>167 (± 5.7)</td>
<td>168 (± 6.0)</td>
<td>169 (± 6.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>67.2 (± 12.8)</td>
<td>66.5 (± 12.5)</td>
<td>67.5 (± 14.0)</td>
<td>66.7 (± 7.9)</td>
<td>0.79</td>
</tr>
<tr>
<td>BMI, kg m⁻²</td>
<td>23.8 (± 4.3)</td>
<td>23.7 (± 4.0)</td>
<td>23.8 (± 4.7)</td>
<td>23.4 (± 2.4)</td>
<td>0.82</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.77 (± 0.06)</td>
<td>0.78 (± 0.06)</td>
<td>0.77 (± 0.06)</td>
<td>0.75 (± 0.04)</td>
<td>0.11</td>
</tr>
<tr>
<td>Breast volume, cm³</td>
<td>880 (± 521)</td>
<td>863 (± 436)</td>
<td>894 (± 598)</td>
<td>875 (± 386)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

CYP17 genotyping was performed in 254 out of the 258 women.

aLinear and logistic regression models were used to compare the effect of one or two A2 alleles on continuous and dichotomous variables, respectively.

b36 women were not able to recall their natural menstrual cycle length, n = 222.

c79 women did not remember the time until regular menstrual periods were established.

dFive of the totally 227 women who had ever used OCs did not provide us with data about duration of OC use, n = 232.

eThe breast volume was measured during menstrual cycle days 18–23. The data include women who were not currently breast feeding or who had had breast surgery.
phase of the menstrual cycle remains relatively constant (Lenton et al., 1984a), whereas the length of the follicular phase can vary considerably (Lenton et al., 1984b), women with short menstrual cycles spend more time in the luteal phase, where both estrogen and progesterone levels are elevated, than in the follicular phase where progesterone levels are low and estrogen levels are increasing. Given that a short menstrual cycle is associated with an increased risk of breast cancer (Kelsey et al., 1993; Olsson et al., 1983; Whelan et al., 1994), especially prior to age 40 years (Terry et al., 2005), the association between the A2 allele and a short menstrual cycle suggests that the CYP17 polymorphism may influence early onset breast cancer risk by modifying menstrual frequency.

To our knowledge, this is the first study to investigate the association between the CYP17 genotype and the OC start age. The high percentage of OC use (92%) among our study participants allowed us to study this association with reasonable precision. Our study showed that each A2 allele was associated with a 7 month earlier A2/A2) that OCs were prescribed to regulate these numbers of A2 alleles. One hypothesis that may explain our finding is when the OC is introduced. Several studies have shown that use of OCs prior to age 20 years significantly increases the risk for early onset breast cancer (Olsson et al., 1989; Velentgas and Daling, 1994; Collaborative Group on Hormonal Factors in Breast Cancer, 1996; Henderson and Feigelson, 2000; Key et al., 2001; Kumle et al., 2002; Mitrunen and Hirvonen, 2003; Jernström, et al., 2005). Our results suggest that use of OCs prior to age 20 years should be taken into consideration when investigating the link between CYP17 genotype and breast cancer.

Table II. The odds ratio (OR) of being a CYP17 A2/A2 carrier varied by BRCA mutation status and was highest among BRCA1/2 non-carriers

<table>
<thead>
<tr>
<th></th>
<th>CYP17 (A1/A1 + A1/A2)</th>
<th>CYP17 (A2/A2)</th>
<th>Adjusted OR (95% CI; P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1/2 non-carriers</td>
<td>(n = 218)</td>
<td>(n = 36)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>14</td>
<td>1.00 ref</td>
</tr>
<tr>
<td>BRCA1/2 carriers</td>
<td>27</td>
<td>3</td>
<td>0.31 (0.09–1.09; P = 0.068)</td>
</tr>
<tr>
<td>BRCA1/2 carriers</td>
<td>97</td>
<td>12</td>
<td>0.34 (0.16–0.75; P = 0.008)</td>
</tr>
<tr>
<td>Untested women</td>
<td>55</td>
<td>7</td>
<td>0.35 (0.14–0.91; P = 0.032)</td>
</tr>
</tbody>
</table>

The CYP17 genotype was missing for four women. The ORs are adjusted for family clustering because several women could belong to the same family. We included women with and without a cancer diagnosis at the time of testing.

The results after addition of the CYP17 genotype for the 77 BRCA1/2 carriers born in 1956 or later with available DNA.

be more detrimental to the breast epithelium the younger the woman is when the OC is introduced. Several studies have shown that use of OCs prior to age 20 years significantly increases the risk for early onset breast cancer (Olsson et al., 1989; Velentgas and Daling, 1994; Collaborative Group on Hormonal Factors in Breast Cancer, 1996; Henderson and Feigelson, 2000; Key et al., 2001; Kumle et al., 2002; Mitrunen and Hirvonen, 2003; Jernström, et al., 2005). Our results suggest that use of OCs prior to age 20 years should be taken into consideration when investigating the link between CYP17 genotype and breast cancer.

To our knowledge, this is the first study to examine the association between BRCA mutation status and the CYP17 genotype in healthy women. The CYP17 A2 variant allele was significantly more common in the group of non-carriers from BRCA1 and BRCA2 families compared with mutation carriers, women from BRCA families and as of yet untested women. This indicates that the CYP17 A2 variant allele does not significantly contribute to the increased breast cancer risk among the BRCA families. Furthermore, the allele frequency was not in Hardy–Weinberg equilibrium in the women from BRCA families. Cui et al. (2003) also reported a deviation from the Hardy–Weinberg equilibrium in case subjects with a family history of breast cancer. The frequency of the A2 variant CYP17 allele in our study is comparable with that of other studies (Mitrunen and Hirvonen, 2003) including a Swedish study of post-menopausal women (Einarsdottir et al., 2005), but higher than in another Swedish population-based series of healthy premenopausal women (41% versus 31%, P = 0.01) (Bergman-Jungström et al., 1999). As the CYP17 A2 variant allele was less common among BRCA1 or BRCA2 mutation carriers compared with non-carriers from the same families, one might hypothesize that the combination of the CYP17 A2/A2 genotype and a BRCA1 or BRCA2 mutation is disadvantageous, especially during fetal development. Studies that have excluded known BRCA1 and BRCA2 mutation carriers (Spurdle et al., 2000; Cui et al., 2003) have found an excess risk of family history with homozygosity for the A2 allele. Conversely, a German study that did not take BRCA1/2 mutation status into account reported fewer homozygous A2 carriers in cases with a family history (Verla-Tebit and Chang-Claude, 2005). Studies investigating the relationship between early onset breast cancer and CYP17 may be biased towards the null hypothesis if women with BRCA1/2 mutations are not examined separately. One recent paper by Yazici et al. (2006) reported that the frequency of the CYP17 A2 allele was significantly higher in ovarian cancer patients without BRCA1/2 mutations. They suggested
that the CYP17 A2 allele polymorphism may confer an increased risk for ovarian cancer and provide a biomarker for ovarian cancer in patients without mutations in the BRCA genes. The increased risk for ovarian cancer in women who are homozygous for the CYP17 A2 allele but lack BRCA1/2 mutations may be mediated through short menstrual cycles. Both the present study and the study by Small et al. (2005) found that short cycles are significantly more common in homozygous CYP17 A2 allele carriers and short cycles are a well-known risk factor for ovarian cancer (Casagrande et al., 1979).

We found no correlation between the CYP17 genotype and age at menarche, nulliparity, age at first full-term pregnancy or variables describing body constitution. Several other studies have shown no association between the CYP17 A2 allele and age at menarche (Dunning et al., 1998; Haiman et al., 1999; Yager, 2000; Lai et al., 2001; Onland-Moret et al., 2005), whereas others have reported A2 allele carriers that have a significantly younger age at menarche (Bang et al., 1991; Moore et al., 1991; Feigelson et al., 1997; Heltzlsouer et al., 1998; Garcia-Closas et al., 2002; Lurie et al., 2005). Mitrunen et al. (2000) reported that the protective effect of late menarche was limited to A1/A1 carriers, although mainly in premenopausal women. Similar results were found by Ambrosone et al. (2003).

To our knowledge, there are only three studies (Feigelson et al., 1997; Bergman-Jungeström et al., 1999; Verla-Tebit et al., 2005) that have found a positive relationship between the CYP17 A2 variant allele and an increased risk for breast cancer. In our study, no such association could be studied because all the women were healthy when they entered the study and to this date only nine women have developed early onset breast cancer. When we genotyped the 77 additional women with BRCA1/2 mutations who were not part of the original study, the A2/A2 genotype was less common among the women with cancer at the time of testing (2 out of 35, i.e. 5.7%) than in women who were healthy at the time of testing (6 out of 42, i.e. 14.3%). The increased risk of breast cancer among A2 allele carriers reported in the previous studies (Feigelson et al., 1997; Bergman-Jungeström et al., 1999; Verla-Tebit et al., 2005) might be partly explained by factors other than the gene itself and that CYP17 modifies the effects of such exposures (Little and Simard, 2005). Such factors might be early age at first OC use, or greater exposure to simultaneously high estrogen and progesterone levels during the luteal phase of the menstrual cycle due to shorter intervals between menstrual periods. Another hypothesis underlying the relationship between the CYP17 genotype and breast cancer, namely that the variant allele A2 brings about increased estrogen levels through increased transcriptional activity (Feigelson et al., 1998; Haiman et al., 1999; Onland-Moret et al., 2005), is controversial. Several studies have shown conflicting associations between the CYP17 polymorphism and levels of estrone, estradiol, estrogen metabolites, progesterone, testosterone, androstenedione, dehydroepiandrosterone sulphate (DHEAS), sex hormone binding globulin (SHBG), follicular stimulating hormone (FSH), and insulin (Dunning et al., 1998; Feigelson et al., 1998; Haiman et al., 1999; Mitrunen et al., 2000; Yager, 2000; Jernström et al., 2001; Garcia-Closas et al., 2002; Travis et al., 2004; Small et al., 2005). Furthermore, Kristensen et al. (1999) showed that the → C polymorphism did not influence binding to Sp-1 sites in vitro.

In conclusion, we found that the CYP17 A2 allele was associated with a short menstrual cycle and an early age at first OC use in this cohort of young women from breast cancer high-risk families. Furthermore, the CYP17 A2 allele does not appear to be associated with the major breast cancer susceptibility genotypes. A short menstrual cycle length, age at first OC use and BRCA mutation status may therefore need to be considered in studies exploring the relationships between CYP17 and risk factors for early onset breast cancer.

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References


