# Steroid Metabolism Gene *CYP17* Polymorphism and the Development of Breast Cancer[1]

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## Abstract

**The potential role of the polymorphism in the *CYP17* gene was evaluated in a case-control study with 483 incident breast cancer patients and 482 population controls, all of homogenous Finnish origin. Our data disagree with the earlier suggestions that the minor *A2* variant of *CYP17* would pose an increased risk for developing advanced breast cancer. In contrast, a tendency of inverse association was found for premenopausal women carrying the *A2* allele containing genotypes with a multivariate adjusted odds ratio of 0.58 approaching statistical significance (95% CI, 0.31–1.07). Agreeing with previous observations, the protective effect of later age at menarche (≥13 years) was mainly limited to women with *A1/A1* genotype, although this could only be seen in premenopausal women (odds ratio, 0.34; 95% CI, 0.15–0.76). Similarly, we found a remarkably lower risk for premenopausal women with at least one child (odds ratio, 0.22; 95% CI, 0.07–0.62) to be mainly attributable to the *A1/A1* genotype. *CYP17* genotypes may thus modify individual breast cancer proneness in certain subpopulations, although they appear not to have any major modifying role in the risk of this malignancy overall. Because these findings are based on relatively small numbers in stratified analysis, they should, however, be interpreted with caution before being confirmed in future studies.**

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## Introduction

Endogenous exposure to circulating steroid hormones appears to be closely related to the development and progression of breast cancer (1). Several factors affecting exposure to endogenous and exogenous sex hormones may modify individual susceptibility to this neoplasm. In agreement with this, early menarche, late menopause, postmenopausal obesity, alcohol consumption, and the use of estrogen replacement therapy have been shown to increase the risk of developing breast cancer, whereas early FFTP,[3] lactation, and physical activity seem to protect from it (1). Recent interest has been focused on polymorphisms in genes that control the metabolism or intracellular transport of sex hormones (2).

The *CYP17* gene codes for the cytochrome P450c17$\alpha$ enzyme, which mediates both steroid 17a-hydroxylase and 17,20-lyase activities and functions at key branch points in human steroidogenesis (3, 4). The 5′ untranslated region of *CYP17* contains a single T (in the *A1* allele) to C (in the *A2* allele) base substitution at position 1931 that creates an additional Sp-1-type (CCACC box) promoter motif between the initiation of translation and transcription start sites (5). It has led to the reasoning that the *A2* allele is associated with enhanced transcriptional activity. Because *CYP17* has a fundamental role in steroid metabolism, it has been further reasoned that this allele may be associated with increased susceptibility to breast cancer.

Recently Feigelson *et al.* (6) found the *A2* allele to be associated with higher serum estrogen and progesterone levels compared with the *A1* allele. Subsequently, they found *A2/A2* carriers to be half as likely current users of hormone replacement therapy compared with women with the *A1/A1* genotype (OR, 0.52; 95% CI, 0.31–0.86; Ref. 7). In another study, women with the *A2/A2* genotype had elevated levels of estrone and dehydroepiandrosterone (8). On the basis of the above studies, the *CYP17* polymorphism could indeed be an important modifier of the corresponding enzyme activity.

As for the potential role of *CYP17* polymorphism in breast cancer risk, the studies completed thus far have given controversial results. In the first study by Feigelson *et al.* (9), the women with *A2* allele-containing genotypes were at 2.5-fold (95% CI, 1.07–5.94) risk for advanced breast cancer compared with the women without the allele. The reduced risk of breast cancer usually associated with a later age at menarche was also observed but was limited to women with the *A1/A1* genotype (OR, 0.47; 95% CI, 0.22–0.98). This observation was recently supported in another study where the respective OR was 0.57 (95% CI, 0.36–0.90; Ref. 8). Recently Bergman-Jungestrom *et al.* (10) reported a significantly increased risk (OR, 2.0; 95% CI, 1.1–3.5) for young women (<37 years) carrying at least one

[3] The abbreviations used are: OR, odds ratio; CI, confidence interval; WHR, waist:hip ratio; BMI, body mass index; FFTP, first full-term pregnancy.

*A2* allele. In another study this allele was associated with a significantly increased risk (OR, 2.10; 95% CI, 1.04–4.27) for male, but not for female, breast cancer (11). The other studies did not show any significant association between *CYP17* genotypes and breast cancer risk (12–16).

Most of the earlier studies have suffered from a small study size, racially diverse study populations, or deficiency of study design in terms of not selecting controls to match the cases by age and menopausal status. This has raised a need for large studies on the potential role of genes encoding for estrogen metabolism and transport enzymes in individual breast cancer proneness, recently emphasized by Coughlin and Piper (17). We further investigated the potential role of *CYP17* polymorphism in breast cancer proneness in a large study population consisting of 483 incident breast cancer patients and 482 healthy population controls, all of homogenous Finnish origin.

## Materials and Methods

**Study Population.** This case-control study is an extension of Kuopio Breast Cancer Study that follows the protocol of the International Collaborative Study of Breast and Colorectal Cancer coordinated by the European Institute of Oncology in Milan. All women with a suspicious breast lump or breast symptoms and living in the study area were invited to Kuopio University Hospital from 1990 to 1995. They were asked to participate in the study at the first hospital examination before either the patient or the interviewer knew the diagnosis. Body-size indicators (height, weight, waist and hip circumference) were recorded at the time of the interview (18). Of the women who agreed to participate in the study, 516 were finally diagnosed with breast cancer, as were 12 of the women who had refused to participate. The participation rate of the cases was thus 98%. Lymphocyte DNA was available for 486 of the patients who had agreed to participate in the study.

Healthy population controls were drawn from the Finnish National Population Register covering the same catchment area of the cases. In all, 514 controls were interviewed in parallel with the cancer cases, for a final participation rate of 72%. Of these, lymphocyte DNA was available for 492 subjects.

Four controls and three cancer cases were excluded from the study because of the poor quality of their DNA. Additionally, we excluded four population controls with earlier breast cancer diagnosis, as well as two controls of non-Finnish origin. Therefore, our final study population contained 483 incident breast cancer cases, and 482 healthy subjects, all Finnish Caucasians.

The malignant breast tumors were categorized on the basis of UICC Tumor-Node-Metastasis classification (19). Women having axillary lymph node-positive disease ($n = 164$) or metastatic breast cancer (stage IV; $n = 16$) at diagnosis were considered advanced cases. The cases diagnosed with a tumor confined to the breast, either *in situ* ($n = 40$) or invasive ($n = 253$), were designated as local. This categorization could not be performed for 10 patients because of missing information on lymph node involvement.

***CYP17* Genotyping.** The *CYP17* genotype was determined by a PCR-based method essentially as described by Feigelson *et al.* (6). Briefly, subsequent to the PCR with specific primers (5′-CAT TCG CAC TCT GGA GTC-3′ and 5′-AGG CTC TTG GGG TAC TTG-3′), 15-$\mu$l aliquots of the amplification products were digested for 2 h at 37°C using *Msp*AI (Promega). Presence of the *Msp*A1 restriction site differentiated the *A2* allele from the *A1* allele, which lacks the site. To ensure the quality of the laboratory analyses, two independent readers interpreted the results, any sample with ambiguous results was reanalyzed, and a random selection of 10% of all samples was repeated. No discrepancies were discovered upon replicate testing.

**Statistical Analysis.** The association between *CYP17* alleles and breast cancer was examined using unconditional logistic regression. All ORs and 95% CIs were adjusted for age (5-year intervals), age at menarche (≤12, 13–14, ≥15 years), age at FFTP (nulliparous, <25, 25–30, >30 years), number of children (continuous), history of benign breast disease (no/yes), first-degree (mother, sister, daughter) family history of breast cancer (no/yes), WHR (≤0.91, >0.91), use of oral contraceptives (never/ever), and postmenopausal use of estrogen (never/ever). If data on any of the adjusting variables was missing, subjects were excluded from the logistic regression analyses.

The putative low-risk genotype *A1/A1* served as a reference category. All analyses were first performed separately for subjects with *A1/A2* and *A2/A2* genotypes. However, as no clear gene dose effects were observed, the *A1/A2* and *A2/A2* genotypes were combined to increase the statistical power in stratified analysis.

All results are shown stratified by menopausal status at the time of the diagnosis of the case patient. Women who reported natural menopause or had undergone bilateral oophorectomy were classified as postmenopausal. Hysterectomized women with intact ovaries/ovary (40 cases, 41 controls) and women for whom the details of the operation were unknown (6 cases, 2 controls) were also classified postmenopausal if they were no longer menstruating and were older than 51 years (median for menopause in Finnish women). All of the others were classified premenopausal. WHR, BMI, and age at FFTP were dichotomized on the basis of the median values for population controls. The methods regarding clinical data and medical history have been described in detail elsewhere (18).

## Results

Because the controls were younger, at 53.5 years (SD, 10.9 years), than the cases at 59.0 years (SD, 14.3 years; $P < 0.001$), the proportion of premenopausal women was higher among population controls (42%) compared with breast cancer patients (34%). The mean age at menarche [13.6 years (SD, 1.5 years for controls), 13.8 years (SD, 1.6 years) for cases] and age at first term pregnancy [24.6 years (SD, 4.1 years) for controls, 24.9 years (SD, 4.6 years) for cases] was similar in both groups. First-degree family history of breast cancer was associated with an increased risk of this malignancy (OR, 2.53; 95% CI, 1.48–4.31; Table 1). Much weaker, but yet significant, associations were observed for the history of benign breast disease (OR, 1.33; 95% CI, 1.01–1.75) and WHRs over 0.91 (OR, 1.38; 95% CI, 1.06–1.81). A significantly decreased risk, on the other hand, was observed for women who reportedly had ever used oral contraceptives (OR, 0.66; 95% CI, 0.48–0.91), and for women with at least one child (OR, 0.53; 95% CI, 0.37–0.77).

The genotype frequencies in control population were in agreement with those predicted under Hardy-Weinberg equilibrium ($P = 0.976$). The distribution of *CYP17* genotypes and the ORs associated with breast cancer are shown in Table 2. The *A2* allele did not significantly affect the breast cancer risk, either when all women were considered together or after stratification by menopausal status. Fifty-eight percent of controls and 59% of cases were carriers of at least one *A2* allele. When stratified by menopausal status, the frequency of subjects with the *A2* allele-containing genotypes appeared higher among both postmenopausal controls (60%) and cases (61%) compared

*Table 1* Selected characteristics of the study subjects

| | Case/control[a] | OR[b] (95% CI) |
|---|---|---|
| Menopausal status | | |
| Premenopausal | 164/204 | 1.0 |
| Postmenopausal | 319/278 | 0.73 (0.42–1.27) |
| Age at menarche | | |
| <13 | 98/101 | 1.0 |
| 13–14 | 219/251 | 0.82 (0.59–1.16) |
| ≥15 | 150/127 | 0.99 (0.68–1.46) |
| Age at FFTP | | |
| Nulliparous | 102/57 | 1.0 |
| ≤25 | 237/263 | 0.55 (0.38–0.81) |
| 26–30 | 94/122 | 0.44 (0.29–0.69) |
| ≥31 | 47/40 | 0.64 (0.36–1.12) |
| Number of full-term pregnancies | | |
| Nulliparous | 102/57 | 1.0 |
| 1 | 68/64 | 0.59 (0.36–0.98) |
| 2 | 141/181 | 0.50 (0.33–0.76) |
| 3+ | 171/180 | 0.54 (0.36–0.80) |
| Use of oral contraceptives | | |
| Never | 313/243 | 1.0 |
| Ever | 164/239 | 0.66 (0.48–0.91) |
| Postmenopausal use of estrogen | | |
| Never | 221/164 | 1.0 |
| Ever | 91/114 | 0.82 (0.58–1.16) |
| WHR | | |
| ≤0.91 | 187/236 | 1.0 |
| >0.91 | 291/243 | 1.38 (1.06–1.81) |
| BMI | | |
| ≤25.4 | 208/240 | 1.0 |
| >25.4 | 260/239 | 1.22 (0.92–1.62) |
| First-degree family history of breast cancer | | |
| No | 424/459 | 1.0 |
| Yes | 54/22 | 2.53 (1.48–4.31) |
| History of benign breast disease | | |
| No | 296/313 | 1.0 |
| Yes | 180/167 | 1.33 (1.01–1.75) |
| Education[c] | | |
| Low | 292/277 | 1.0 |
| Medium | 127/135 | 1.11 (0.81–1.52) |
| High | 62/69 | 1.19 (0.78–1.80) |
| Current alcohol intake | | |
| Never | 271/206 | 1.0 |
| Once a month or less | 134/187 | 0.74 (0.54–1.01) |
| Daily–weekly | 75/89 | 0.87 (0.59–1.29) |
| Smoking habits | | |
| Never | 363/351 | 1.0 |
| Ex-smoker | 52/67 | 0.94 (0.62–1.41) |
| Current smoker | 64/64 | 1.34 (0.87–1.93) |

[a] Total number of cases and controls does not correspond because of missing values.
[b] Adjusted for age.
[c] Low: none or primary school; medium: junior high school, college or corresponding; high: senior high school, trade school, or university.

with the respective frequencies (57% and 53%) in the premenopausal subjects, the latter difference approaching statistical significance ($P = 0.069$). Therefore all additional analyses were performed separately for pre- and postmenopausal women.

When case patients were considered by the tumor stage, premenopausal patients having advanced disease were less frequently carriers of the *A2* allele containing genotypes (48%) compared with controls (56%; Table 3). There was a clear tendency of lower risk of this breast cancer type in carriers of *A2* allele with a multivariate adjusted OR of 0.58 approaching statistical significance (95% CI, 0.31–1.07). In contrast, in postmenopausal cases no such tendency was observed (OR, 0.99; 95% CI, 0.57–1.69). The *CYP17* genotypes were similarly distributed among pre- and postmenopausal cases and among controls with a diagnosis of local cancer (no nodes involved). Furthermore, no significant associations were observed after stratifying by estrogen- or progesterone-receptor status (data not shown), although postmenopausal progesterone receptor-positive patients were more likely to carry at least one *A2* allele (69%) compared with receptor negative patients (56%; $P = 0.027$). A similar tendency was seen between postmenopausal estrogen receptor-positive (66%) and -negative patients (52%; $P = 0.077$).

Association between potential hormone-related breast cancer risk factors and the *CYP17* genotype was assessed by stratified analysis (Table 4). The protective effect of late age at menarche (≥13 years) was more pronounced among premenopausal women with *A1/A1* genotype (OR, 0.34; 95% CI, 0.15–0.76; $P$ for interaction = 0.10). This effect could not be seen when pre- and postmenopausal women were considered together (OR, 1.25; 95% CI, 0.74–2.09). An especially low risk (OR, 0.22; 95% CI, 0.07–0.62) was observed for premenopausal women with at least one child and the *A1/A1* genotype ($P$ for interaction = 0.11). In contrast, an increased risk of breast cancer with borderline significance (OR, 1.7; 95% CI, 0.98–2.94) was observed for postmenopausal women with *A1/A2* or *A2/A2* genotype and BMIs over 25.4 kg/m$^2$. The risks associated with postmenopausal use of estrogen, use of oral contraceptives, age at FFTP, and WHR were not modified by the *CYP17* genotype.

## Discussion

In agreement with the majority of the previous studies on *CYP17* polymorphism and breast cancer risk, this study did not reveal any significant association between the *CYP17 A2* allele and overall risk of breast cancer in Finnish population. However, agreeing with the findings of Feigelson *et al.* (9) and Haiman *et al.* (8), we found the protective effect of later age at menarche to be mainly attributable to women with the *A1/A1* genotype. Weston *et al.* (16) also reported a similar trend, although it failed to reach statistical significance. In our study population, the effect was seen only among premenopausal women, whereas in the above studies, the association was for the whole population. These findings are opposite to those of Helzlsouer *et al.* (13), who observed a trend of decreasing risk with later age at menarche among women with the *A2* allele. This association was, however, far from statistically significant, and the number of cases and controls was relatively small in their study. On the other hand, Dunning *et al.* (12) saw no difference in the risk associated with the age at menarche between different genotype groups.

Similarly to later age at menarche, the benefit of having children was found only among the premenopausal women with the *A1/A1* genotype (OR, 0.22; 95% CI, 0.07–0.62). This observation is compatible with the hypothesis that the protection against breast cancer is reduced among women with the *A2* allele containing genotypes because of elevated baseline levels of circulating steroid hormones. Contrasting the finding of Haiman *et al.* (8), the same was not found for the earlier age at FFTP.

It should be noted that even if our study contained a reasonably large sample size, the number of subjects in the subgroup analysis was relatively low. The findings should thus be interpreted with caution before confirmed in future studies.

As the above-described significant associations were

*Table 2* Associations between *CYP17* genotype and breast cancer according to menopausal status at diagnosis of the case patient

| | *A1/A1* | *A1/A2* | *A2/A2* | *A1/A2* and *A2/A2* |
|---|---|---|---|---|
| All | | | | |
| Cases, *n* (%) | 199 (41.5) | 227 (47.4) | 53 (11.1) | 280 (58.5) |
| Controls, *n* (%) | 200 (41.7) | 220 (45.8) | 60 (12.5) | 280 (58.3) |
| OR (95% CI)[a] | 1.0 | 0.96 (0.71–1.28) | 0.79 (0.50–1.26)[b] | 0.92 (0.69–1.22) |
| Menopausal status at diagnosis | | | | |
| Premenopausal | | | | |
| Cases, *n* (%) | 77 (47.2) | 71 (43.6) | 15 (9.2) | 86 (52.8) |
| Controls, *n* (%) | 88 (43.3) | 88 (43.3) | 27 (13.3) | 115 (56.7) |
| OR (95% CI)[a] | 1.0 | 0.87 (0.54–1.39) | 0.63 (0.30–1.32)[b] | 0.81 (0.52–1.27) |
| Postmenopausal | | | | |
| Cases, *n* (%) | 122 (38.6) | 156 (49.4) | 38 (12.0) | 194 (61.4) |
| Controls, *n* (%) | 112 (40.4) | 132 (47.7) | 33 (11.9) | 165 (59.6) |
| OR (95% CI)[a] | 1.0 | 1.00 (0.68–1.48) | 0.98 (0.53–1.80)[b] | 1.00 (0.69–1.45) |

[a] Adjusted for age, age at menarche, age at FFTP, number of full term pregnancies, first-degree family history of breast cancer, history of benign breast disease, use of oral contraceptives, WHR, and postmenopausal use of estrogen.
[b] *P* for trend: all, 0.228; premenopausal, 0.381; postmenopausal, 0.961.

*Table 3* Number of breast cancer cases and controls, and ORs[a] associated with *CYP17* polymorphism by menopausal status and tumor stage

| | *A1/A1* | *A1/A2* | *A2/A2* | *A1/A2* and *A2/A2* |
|---|---|---|---|---|
| Premenopausal | | | | |
| Controls, *n* (%) | 88 (43.3) | 88 (43.3) | 27 (13.3) | 115 (56.7) |
| Cases by stage | | | | |
| Local, *n* (%) | 42 (43.8) | 44 (45.8) | 10 (10.4) | 54 (56.2) |
| OR (95% CI) | 1.0[b] | 1.02 (0.59–1.76) | 0.73 (0.31–1.72)[c] | 0.95 (0.56–1.60) |
| Advanced, *n* (%) | 35 (52.2) | 27 (40.3) | 5 (7.5) | 32 (47.8) |
| OR (95% CI) | 1.0[b] | 0.62 (0.32–1.20) | 0.43 (0.14–1.27)[d] | 0.58 (0.31–1.07) |
| Postmenopausal | | | | |
| Controls, *n* (%) | 112 (40.4) | 132 (47.7) | 33 (11.9) | 165 (59.6) |
| Cases by stage[e] | | | | |
| Local, *n* (%) | 78 (40.2) | 90 (46.4) | 26 (13.4) | 116 (59.8) |
| OR (95% CI) | 1.0[b] | 1.02 (0.65–1.60) | 1.09 (0.55–2.16)[f] | 1.03 (0.67–1.59) |
| Advanced, *n* (%) | 39 (34.8) | 63 (56.3) | 10 (8.9) | 73 (65.2) |
| OR (95% CI) | 1.0[b] | 1.02 (0.58–1.79) | 0.86 (0.34–2.18)[g] | 0.99 (0.57–1.69) |

[a] Adjusted for age, age at menarche, age at FFTP, number of full term pregnancies, first-degree family history of breast cancer, history of benign breast disease, use of oral contraceptives, WHR, and postmenopausal use of estrogen.
[b] Subjects with *A1/A1* genotype serve as the reference category.
[c] *P* for trend = 0.593.
[d] *P* for trend = 0.059.
[e] Total number does not correspond because the stage of the disease could not be classified for 10 patients because of missing information on lymph node involvement.
[f] *P* for trend = 0.830.
[g] *P* for trend = 0.832.

mainly confined to premenopausal women, this supports the view that the etiology of breast cancer may differ by menopausal status. The menopausal status should thus be taken properly into account in the analyses. However, in the study of Weston *et al.* (16) with 363 cases and 240 patient controls of Caucasian, African-American, and Latino origin, no detailed data were given about the potential effect of menopausal status. In the study by Kristensen *et al.* (15) including 510 Norwegian cases and 210 controls, the controls were 20–44 years old (*i.e.*, mostly premenopausal), whereas the cases were 27–91 years old (*i.e.*, both pre- and postmenopausal). Inversely, in the largest study done thus far, by Dunning *et al.* (12), the breast cancer patients ($n = 835$) were all diagnosed under the age of 55 years (*i.e.*, mostly premenopausal), whereas the age at diagnosis of the controls ($n = 591$) varied between 45 and 74 years (*i.e.*, both pre- and postmenopausal). They acknowledged the problem, especially because the positive findings of Feigelson *et al.* (9) were from considerably older cases (63 years) and controls (61 years), and stressed the possibility that *CYP17* genotype effects might be age-specific with marked effects seen only among older cases, raising a need for additional studies involving older study subjects. However, the present study included relatively large group of postmenopausal subjects with mean ages of 61 years and 66 years for the controls and cases, respectively, but no significant genotype effects were seen.

Although there was a clear tendency of lower risk of advanced breast cancer in carriers of at least one *A2* allele, the association did not reach statistical significance. Moreover, the *A2* allele-containing genotypes were not significantly associated with disease status (local *versus* advanced) among the cases. We therefore cannot totally rule out the possibility that the apparent effect modification by disease status was a chance finding. This remains to be evaluated in future studies.

Excluding the above study of Dunning *et al.* (12), one weakness in the previous studies was their small study size. Despite being one of the largest, our study barely reached the 90% power at the 5% significance level to detect a 1.5-fold moderate effect in the risk associated with the variant allele. Most of the previous studies included considerably smaller study populations than ours and may thus have lacked statistical

*Table 4* Association between *CYP17* genotypes and breast cancer risk stratified by selected characteristics

| | Premenopausal | | | | Postmenopausal | | | |
|---|---|---|---|---|---|---|---|---|
| | *A1/A1* | | *A1/A2* and *A2/A2* | | *A1/A1* | | *A1/A2* and *A2/A2* | |
| | Case/control | OR[a] (95% CI) | Case/control | OR[a] (95% CI) | Case/control | OR[a] (95% CI) | Case/control | OR[a] (95% CI) |
| Age at menarche | | | | | | | | |
| <13 yr | 25/16 | 1.0 | 24/29 | 1.0 | 19/28 | 1.0 | 30/28 | 1.0 |
| ≥13 yr | 52/72 | 0.34 (0.15–0.76) | 62/86 | 0.82 (0.42–1.63) | 96/83 | 1.49 (0.72–3.10) | 155/135 | 0.99 (0.52–1.89) |
| Postmenopausal use of estrogen | | | | | | | | |
| Never | | | | | 86/69 | 1.0 | 134/94 | 1.0 |
| Ever | | | | | 33/43 | 1.14 (0.59–2.18) | 56/71 | 0.85 (0.51–1.42) |
| Use of oral contraceptives | | | | | | | | |
| Never | 24/24 | 1.0 | 32/28 | 1.0 | 92/76 | 1.0 | 164/114 | 1.0 |
| Ever | 53/64 | 1.15 (0.49–2.72) | 54/87 | 0.56 (0.28–1.10) | 27/36 | 0.82 (0.38–1.77) | 27/51 | 0.56 (0.29–1.08) |
| Parity | | | | | | | | |
| Nulliparous | 18/7 | 1.0 | 12/13 | 1.0 | 27/15 | 1.0 | 45/22 | 1.0 |
| Parous | 59/81 | 0.22 (0.07–0.62) | 74/102 | 0.79 (0.31–2.02) | 95/97 | 0.58 (0.25–1.31) | 148/143 | 0.66 (0.35–1.24) |
| Age at FFTP for parous women | | | | | | | | |
| ≤23 yr | 29/32 | 1.0 | 31/45 | 1.0 | 41/43 | 1.0 | 64/80 | 1.0 |
| >24 yr | 30/49 | 0.83 (0.39–1.79) | 43/57 | 1.35 (0.69–2.64) | 54/54 | 0.89 (0.45–1.77) | 82/63 | 1.45 (0.82–2.59) |
| BMI | | | | | | | | |
| ≤25.4 | 53/57 | 1.0 | 47/68 | 1.0 | 45/45 | 1.0 | 62/69 | 1.0 |
| >25.4 | 24/30 | 0.63 (0.27–1.43) | 39/46 | 1.03 (0.53–2.01) | 71/67 | 1.38 (0.70–2.70) | 123/95 | 1.70 (0.98–2.94) |
| WHR | | | | | | | | |
| <0.91 | 35/52 | 1.0 | 36/61 | 1.0 | 40/51 | 1.0 | 74/72 | 1.0 |
| ≥0.91 | 41/35 | 1.66 (0.83–3.34) | 50/53 | 1.52 (0.83–2.81) | 79/60 | 1.70 (0.93–3.11) | 119/93 | 1.13 (0.69–1.85) |

[a] Adjusted for age, age at menarche, age at FFTP, number of full term pregnancies, first-degree family history of breast cancer, history of benign breast disease, use of oral contraceptives, WHR, and postmenopausal use of estrogen.

power for reliable interpretations. Evidently, larger studies are thus needed to obtain more precise risk estimates.

Because the genotype effects have been shown to differ by race, ethnically mixed study populations are also anticipated to be a potential source of bias in the previous studies. More studies in ethnically diverse but homogenous study populations are thus needed. In this respect, one of the strengths of our study may be the inclusion of only cases and controls who were confirmed to be of genetically homogenous Finnish origin.

It has to be noted that the original study of Feigelson *et al.* (9), showing a 2.5-fold (95% CI, 1.07–5.94) increased risk for advanced breast cancer, suffered from all of the above-mentioned weaknesses, *i.e.*, included racially mixed cases and controls, had relatively small study size, and lacked information on the menopausal status of the subjects. The two other positive findings, on the other hand, were for specific subgroups, *i.e.*, for young (<37 years) females (10), and male breast cancer (11). The evidence for *CYP17* genotype contributing in the overall breast cancer risk is thus relatively weak, further suggesting a minor role for this gene in the etiology of breast cancer.

To conclude, our findings suggest that *CYP17* polymorphism has no major effect in overall breast cancer proneness, but may modify the risk of breast cancer for certain subgroups.

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