Introduction
Breast cancer is a hormone-related cancer, as are cancers of the endometrium, ovary, and prostate [1]. Although the molecular mechanisms involved in initiation and progression are poorly understood, there is evidence that extracellular levels of androgens are associated with the risk of breast cancer.

A49T = codon 49 alanine to threonine substitution; BMI = body mass index; bp = base pairs; CI = confidence interval; L/L = leucine/leucine; OR = odds ratio; PCR = polymerase chain reaction; SRD5A2 = steroid 5α-reductase type II; V89L = codon 89 valine to leucine substitution; V/L = valine/leucine; V/V = valine/valine.
development of breast cancer [2,3]. Nested case–control studies have shown that increased circulating levels of testosterone elevate the risk of breast cancer [4–6]. Experimental studies suggest, however, that androgens exert a potent antiproliferative effect on the growth of several hormone-sensitive human breast cancer cells under both basal and estrogen-induced incubation conditions in vitro [7], as well as in vivo, using ZR-75-1 human breast cancer cells in nude mice [8]. Androgens have been used for the treatment of breast cancer [9,10].

Steroid 5α-reductase converts testosterone to the metabolically more active dihydrotestosterone, which has two isoforms; type I expressed in liver, skin and scalp by SRD5A1 located on chromosome 5; and type II expressed in prostate by SRD5A2 on chromosome 2. In human breast invasive ductal carcinomas, both type I (58% of 60 cases) and type II (15% of 60 cases) are reportedly expressed [11].

The SRD5A2 gene consists of five exons and four introns, and encodes a 254 amino acid protein [12]. Several single nucleotide polymorphisms have been reported in the five exons [13]. However, only two of these polymorphisms (A49T and V89L), along with the variable number of dinucleotide TA repeat polymorphisms in the 3’ untranslated region, have been examined concerning risk and prognosis of cancers.

The V89L polymorphism that substitutes leucine for valine at codon 89 is reported to reduce almost 30% of androstenediol glucuronide, a serum marker of 5α-reductase activity, among Asians [14]. Among Caucasian men, a 10% insignificantly lower androstanediol glucuronide level was observed for individuals with the L/L genotype [15].

The TA repeat polymorphism reportedly has 10 alleles with 0, 8, 9, 10, 17, 18, 19, 20, 21, and 22 repeats, among which the 0-repeat allele (designated TA(0)) and the 9-repeat allele (designated TA(9)) are common. The alleles with more than 10 repeats were found exclusively in African-Americans, the highest risk ethnic group of prostate cancer [16]. No significant difference in serum androstenediol glucuronide level was observed between the TA(0/0) and TA(0/9) genotypes among the Chinese [17].

In the A49T polymorphism that substitutes threonine for alanine at codon 49, the T allele was reported to be the allele with the higher enzyme activity [18].

A49T, V89L and TA repeat polymorphisms could be associated with risk of breast cancer. To our knowledge, however, there have been no studies on the potential association between SRD5A2 gene polymorphisms and breast cancer risk except for one study of the TA repeat polymorphism, which demonstrated no significant difference in the genotype distribution between 141 cases and 70 controls [19]. However, several studies for prostate cancer risk have been reported [17,18,20–26]. Two reports have been published by the same research group in Italy concerning roles in breast cancer prognosis, one regarding the TA repeats [19] and the other regarding the V89L polymorphism [27].

The present study aims to examine the associations between three polymorphisms of SRD5A2 and breast cancer risk for Japanese women using a prevalent case–control study conducted at Aichi Cancer Center.

Materials and methods

Study population

The cases were female breast cancer patients visited at Aichi Cancer Center Hospital [28]. Between March 1999 and April 2000, 247 breast cancer cases were interviewed, and 243 were enrolled. Two patients refused to provide a blood sample after enrollment, and two blood samples were not stored. Among the 239 blood samples, two samples of extracted DNA had concentrations too low to be genotyped. The remaining 237 samples were used in the present study. The pathology of breast tumors was examined for 204 cases at Aichi Cancer Center Hospital, and for 33 cases at other hospitals.

The controls were 187 female cancer-free outpatients, mainly presenting at the clinics for gastroenterology, breast surgery, and gynecology of Aichi Cancer Center Hospital. They were also invited during March 1999 and April 2000. One serum sample was not stored, and one had too low a DNA concentration to be genotyped. Only 185 controls were therefore available.

All participants were given a self-administered questionnaire. Information was requested on demography, family history of breast cancer (mother and/or sisters), and food intake before the appearance of symptoms. Interviewers checked all written responses to ensure that there were no unanswered questions at the time of questionnaire collection.

Genetic analyses

PCR amplification of the A49T polymorphism was conducted by a PCR with confronting two-pair primers method [29], using the following primers: 5′-GCG GAC ACG GGT GGC GTC-3′, 5′-GAA CCA GGC GGC GCG GGT-3′, 5′-GCG GCT ACC CGC CTG CCA G-3′, and 5′-CGC CGG GAG CAG GGC AGT-3′. Aliquots of 30–100 ng genomic DNA were mixed with 25 µl reaction liquid containing 0.18 mmol/l dNTPs, 12.5 pmol each primer, 0.5 units AmpliTaq Gold, and 2.5 µl GeneAmp 10× PCR buffer with 15 mmol/l MgCl2 (Perkin-Elmer Corporation, Foster City, CA, USA). Amplification conditions were set as follows: a 10-min initial denaturation at 95°C,
followed by 30 cycles at 95°C for 1 min denaturation, 64°C for 1 min annealing and 72°C for 1 min extension, and the final extension was at 72°C for 5 min. Genotyping was 403 and 209 bp for the alanine (A) allele, and 430 and 257 bp for the threonine (T) allele.

V89L polymorphisms were genotyped by a PCR-restriction fragment length polymorphism method described by Yamada et al. [24].

Genotypes of the TA repeat polymorphism were determined using the primers 5′-GCT GAT GAA AAC TGT CAA GCT-3′ and 5′-ACT CTA AGC AGA CAC CAC TCA G-3′, with PCR conditions the same as for the A49T polymorphism except for annealing at 54°C. Amplified DNA was 129 bp for the TA(0) allele and 147 bp for the TA(9) allele. Genotyping was confirmed for two samples of TA(0/0) and TA(9/9) by DNA sequencing.

Statistical methods
The Stata 7.0 software package (STATA Corp., College Station, TX, USA) was used to analyze the results, with the Pearson chi-square test employed to compare the distribution of characteristics between cases and controls. ORs and 95% CIs were estimated by unconditional logistic regression analysis.

Results
Characteristics of the study subjects
Our research included 237 female breast cancer cases and 185 female controls. The means and the standard deviations of age were 50.5 ± 8.5 years for cases and 52.9 ± 10.2 years for controls. The other characteristics of cases and controls are summarized in Table 1. No differences in the distributions were observed between cases and controls, except for the menopause state (women without menstruation caused by medication or surgery were included in the premenopause group if aged <50 years) and family history of breast cancer (mother and/or sisters).

Distributions of SRD5A2 polymorphisms and crude ORs
Table 2 presents the distributions of SRD5A2 polymorphisms. All subjects were found to have the A/A genotype for A49T polymorphism.

Two cases and two controls could not be genotyped for the V89L polymorphism. Frequencies of the L/L, V/L and V/V genotypes were 21.7, 52.3, and 26.0% for cases, and 32.8, 43.2, and 24.0% for controls, respectively. Compared with the V/V genotype, the L/L genotype demonstrated a marginally significant OR of 0.61 (95% CI = 0.36–1.05). Table 3 presents the results of the subgroup analysis. Although not significant, women with the L/L genotype had a reduced risk in any subgroup except those with a family history of breast cancer. There was no difference in the OR between premenopausal women and postmenopausal women. The significance of OR was marginal among the body mass index (BMI) < 22 group.

The present study found only two types of TA repeat alleles: TA(0) and TA(9). The frequencies of the TA(0/0), TA(0/9) and TA(9/9) genotypes were 75.9, 22.8, and 1.3% for cases, and 75.1, 22.7, and 2.2% for controls, respectively. No reduction in the OR was found for the TA(0/9) genotype, and women with genotype TA(9/9) were too few to be evaluated (Table 2). The difference in the OR was not observed between premenopausal women (OR = 0.85, 95% CI = 0.43–1.66 for TA(0/9) + TA(9/9) relative to TA(0/0)) and postmenopausal women (OR = 1.09, 95% CI = 0.59–2.01). Accordingly, no subgroup analysis was conducted.

SRD5A2 polymorphisms and risk factors
The associations of the polymorphism genotypes with age at menarche, age at menopause, and BMI were examined among the present controls. No associations were
Table 2

Genotype distributions of A49T, V89L and TA repeat polymorphisms

| Genotype    | Cases     | Controls   | Crude odds ratio | 95% Confidence interval |
|-------------|-----------|------------|------------------|-------------------------|
| A49T        |           |            |                  |                         |
| A/A         | 237 (100) | 185 (100)  | –                | –                       |
| V89L        |           |            |                  |                         |
| V/V         | 61 (26.0) | 44 (24.0)  | 1.00             | Reference               |
| V/L         | 123 (52.3)| 79 (43.2)  | 1.12             | 0.70–1.81               |
| L/L         | 51 (21.7) | 60 (32.8)  | 0.61             | 0.36–1.05               |
| V/L+L/L     | 174 (75.0)| 139 (76.0)| 0.90             | 0.58–1.41               |
| TA repeats  |           |            |                  |                         |
| 0/0         | 180 (75.9)| 139 (75.1)| 1.00             | Reference               |
| 0/9         | 54 (22.8) | 42 (22.7)  | 0.99             | 0.63–1.57               |
| 9/9         | 3 (1.3)   | 4 (2.2)    | 0.58             | 0.13–2.63               |
| 0/9+9/9     | 57 (24.1) | 46 (24.9)  | 0.96             | 0.61–1.50               |

Percentages are shown in parentheses.

Table 3

Crude odds ratios and 95% confidence intervals for V89L polymorphism by subgroup

| Subgroup                  | V/V        | V/L        | L/L        | V/L + L/L |
|---------------------------|------------|------------|------------|-----------|
| Age at diagnosis          |            |            |            |           |
| < 45 years                | 1.00       | 0.71 (0.25–1.99) | 0.45 (0.14–1.52) | 0.62 (0.23–1.64) |
| ≥ 45 years                | 1.00       | 1.28 (0.74–2.21) | 0.70 (0.37–1.22) | 1.00 (0.61–1.67) |
| Body mass index           |            |            |            |           |
| < 22 kg/m²                | 1.00       | 1.06 (0.55–2.06) | 0.48 (0.23–1.00) | 0.80 (0.43–1.48) |
| ≥ 22 kg/m²                | 1.00       | 1.19 (0.59–2.38) | 0.82 (0.37–1.79) | 1.04 (0.54–1.99) |
| Age at menarche           |            |            |            |           |
| < 14 years                | 1.00       | 1.36 (0.67–2.75) | 0.76 (0.35–1.66) | 1.10 (0.56–2.13) |
| ≥ 14 years                | 1.00       | 0.97 (0.50–1.88) | 0.51 (0.24–1.09) | 0.78 (0.42–1.43) |
| Age at first birth        |            |            |            |           |
| < 25 years                | 1.00       | 1.08 (0.49–2.38) | 0.60 (0.25–1.44) | 0.87 (0.42–1.82) |
| ≥ 25 years                | 1.00       | 1.24 (0.64–2.42) | 0.67 (0.31–1.42) | 0.99 (0.53–1.85) |
| No birth                  | 1.00       | 0.78 (0.18–3.36) | 0.43 (0.08–2.17) | 0.63 (0.16–2.46) |
| Number of births          |            |            |            |           |
| < 2                       | 1.00       | 0.81 (0.27–2.38) | 0.40 (0.12–1.32) | 0.63 (0.23–1.74) |
| ≥ 2                       | 1.00       | 1.22 (0.71–2.08) | 0.68 (0.37–1.25) | 0.99 (0.60–1.63) |
| Menopause state           |            |            |            |           |
| Premenopause              | 1.00       | 1.01 (0.49–2.09) | 0.67 (0.29–1.52) | 0.88 (0.45–1.74) |
| Postmenopause             | 1.00       | 1.16 (0.60–2.23) | 0.56 (0.27–1.18) | 0.88 (0.48–1.62) |
| Alcohol                   |            |            |            |           |
| < 1 day/week              | 1.00       | 1.19 (0.69–2.05) | 0.66 (0.36–1.22) | 0.97 (0.58–1.60) |
| ≥ 1 day/week              | 1.00       | 0.94 (0.33–2.65) | 0.48 (0.15–1.50) | 0.72 (0.28–1.88) |
| Smoking                   |            |            |            |           |
| Noncurrent                | 1.00       | 1.29 (0.78–2.13) | 0.64 (0.36–1.12) | 1.00 (0.63–1.59) |
| Current                   | 1.00       | 0.16 (0.02–1.51) | 0.20 (0.02–2.18) | 0.17 (0.02–1.55) |
| Family history of breast cancer |            |            |            |           |
| No                        | 1.00       | 1.22 (0.73–2.03) | 0.59 (0.33–1.05) | 0.95 (0.59–1.52) |
| Yes                       | 1.00       | 0.73 (0.15–3.50) | 1.09 (0.19–6.20) | 0.86 (0.21–3.54) |
observed with mean ages at menarche and at menopause. Mean age at menarche (standard deviation) was 13.6 years (1.5 years) for the V/V genotype, 13.7 years (1.8 years) for the V/L genotype, 13.7 years (1.8 years) for the TA(0/0) genotype, 13.7 years (1.6 years) for the TA(0/9) genotype, and 13.5 years (2.4 years) for the TA(9/9) genotype. Among control women with natural menopause, the mean age at menopause (standard deviation) was 50.5 years (2.7 years) for the V/V genotype, 50.1 years (3.8 years) for the V/L genotype, 50.1 years (3.6 years) for the L/L genotype, 50.8 years (3.7 years) for the TA(0/0) genotype, 49.6 years (2.6 years) for the TA(0/9) genotype, and there were no postmenopausal controls with the TA(9/9) genotype.

Mean BMI (standard deviation) was also similar among the subgroups according to genotype except for four women with the TA(9/9) genotype: 22.5 (3.1), 22.2 (3.0), and 21.9 (3.1), and 19.7 (0.4) for the TA repeat polymorphism, respectively.

**Table 4**

| Genotype distributions of V89L and TA repeat polymorphisms |
|----------------------------------------------------------|
| TA genotype   | V89L genotype (%) | Total |
|---------------|-------------------|-------|
|               | V/V               |       |
| Cases         | 39 (16.6)         | 51 (21.7) | 178 (75.7) |
| TA(0/0)       | 19 (8.1)          | 0 (0.0)  | 54 (23.0)  |
| TA(0/9)       | 3 (1.3)           | 0 (0.0)  | 3 (1.3)    |
| Total         | 61 (26.0)         | 123 (52.3) | 235 (100.0) |
| Controls      | 21 (11.5)         | 60 (32.8) | 138 (75.4) |
| TA(0/0)       | 19 (10.4)         | 22 (12.0) | 41 (22.4)  |
| TA(0/9)       | 4 (2.2)           | 0 (0.0)  | 4 (2.2)    |
| Total         | 44 (24.0)         | 79 (43.2) | 183 (100.0) |

Percentages are shown in parentheses.

**Table 5**

| Combined genotype | Cases (n = 235) | Controls (n = 185) | Odds ratio (95% confidence interval) |
|-------------------|----------------|-------------------|-------------------------------------|
|                   |                |                   | Crude                               |
|                   |                |                   | Adjusted*                           |
| V89L   | TA repeat |         |          |          |          |
| V/V    | 0/0      | 39     | 21      | 1.00     | 1.00     |
| V/L    | 0/0      | 88     | 57      | 0.83 (0.44–1.56) | 0.78 (0.41–1.49) |
| L/L    | 0/0      | 51     | 60      | 0.46 (0.24–0.88) | 0.45 (0.23–0.87) |
| V/V    | 0/9      | 19     | 19      | 0.54 (0.24–1.23) | 0.49 (0.21–1.15) |
| V/L    | 0/9      | 35     | 22      | 0.86 (0.40–1.82) | 0.91 (0.42–1.96) |
| V/V    | 9/9      | 3      | 4       | 0.40 (0.08–1.98) | 0.34 (0.07–1.79) |

Data presented as odds ratio (95% confidence interval). * Adjusting for family history of breast cancer and menopause state.

**Relationship between V89L and TA repeat genotypes**

The combined genotype frequency between TA repeat and V89L polymorphisms was also examined (Table 4). The V/V genotype among controls was 15.2% (21/138) for the TA(0/0) genotype, 46.3% (19/41) for the TA(0/9) genotype, and 100% (4/4) for the TA(9/9) genotype, while among cases was 21.9% (39/178), 35.2% (19/54), and 100% (3/3), respectively. Fisher’s exact test for 3 × 3 tables showed a significant association between the two genotype distributions both among cases and controls (P < 0.001).

**ORs for the combination of V89L and TA repeat polymorphisms**

Table 5 presents the ORs for each combination of the two polymorphisms relative to women with the V/V and TA(0/0) genotypes, who had the highest risk of breast cancer. The combination of L/L and TA(0/0) had a significantly decreased risk, with an OR of 0.46 (95% CI = 0.24–0.88), and the combination of V/V and TA(9/9) showed the lowest, but insignificant, OR. The other three combinations indicated an intermediately reduced risk.

**Discussion**

Although one study reported that the effect of testosterone was cancelled by the adjustment of the estradiol level [30], several studies have provided epidemiological evidence that the serum level of testosterone is associated with the risk of breast cancer [2,4–6]. On the contrary, experimental data propose evidence that androgens are protective against breast cancer [7–10]. The present polymorphism study added the finding that the SRD5A2 genotypes with a lower enzyme activity may reduce the breast cancer risk.
Since the difference in enzyme activity by the genotypes was explained in the Introduction, the potential impact on hormone concentrations should be discussed. Although hormone levels are determined by activities of several enzymes and the influence of the genotypes may differ between females and males, the V89L L/L genotype with low activity was found in Chinese men to be associated with a significantly higher concentration of testosterone, but not with dihydrotestosterone concentration [17]. In British men, the genotype had a significant association with a lower serum level of testosterone and free testosterone [15]. The present study suggests that the L/L genotype might decrease the risk for breast cancer, especially among women with BMI < 22 (Table 3). The L/L genotype was reported to be more frequent in Asian men (21.6%, n = 102) than in Caucasian men (4.1%, n = 49) and African-American men (3.2%, n = 95) [14], which may partly explain the low incidence in breast cancer among Asian women.

Of the TA repeat alleles, only TA(0) and TA(9) were observed in our subjects. The present genotype frequency for Japanese women was similar to those in Italy (n = 70; 79% for TA(0/0), 17% for TA(0/9), and 4% for TA(9/9)) [19], in the United States (n = 802; 75% for TA(0/0), 22% for TA(0/9), and 2% for TA(9/9)) [20], and in China (n = 304; 82% for TA(0/0), 17% for TA(0/9), and 1% for TA(9/9)) [17].

The present study demonstrated a tendency for risk reduction with the TA(9/9) genotype compared with the TA(0/0) genotype (Table 2). In a small-sized study with 141 cases and 70 controls in Italy, there was no significant association between the TA repeat polymorphism and risk of breast cancer [19], while the TA(0/9) or the TA(9/9) genotype demonstrates a reduction in the risk for relapse (P = 0.043). The combination analysis of TA repeat and V89L polymorphisms suggested that women with the TA(0/0) and V/V genotypes had the highest risk for breast cancer (Table 5). This is a plausible finding biologically, because the genotype is regarded to have the highest enzyme activity. There are no studies that examine the joint effect on prostate cancer.

The lack of alanine to threonine substitution in SRD5A2 codon 49 in our subjects is in accordance with a previous study in Japan [24] and another in China [17], suggesting that the T allele may not exist among Asians. The reported frequency of the T allele was 1.0% of 522 alleles for African-American men and 2.3% of 400 alleles for Hispanic men [18]. In Finland, individuals with the T allele were 5.8% (n = 588) for donated blood and cancer-free autopsy samples [26]. The absence of the T allele among Asians may indicate that the polymorphism occurred relatively recently in comparison with V89L and TA repeat polymorphisms. For examining the effects of V89L and TA repeat polymorphisms, our subjects had an advantage in that there was no need to consider the potential effect of A49T as a confounder or a modifier.

The present study demonstrates that the TA(9) allele only coexisted with the V allele (Table 4). The absence of the TA(9/9)–L/L genotype indicated a strong linkage disequilibrium. Another study in Italy unearthed the same result [27].

Conclusions

The present study suggests an reduced risk of breast cancer among women without the genotype combination of SRD5A2 V/V and TA(0/0). An absence of the genotypes necessitating the L–TA(9) haplotype indicated linkage disequilibrium between V89L and TA repeat polymorphisms. There appears to be no substitution of alanine to threonine in codon 49 among the Japanese. Since the metabolic pathway of steroid hormones is complicatedly regulated, activity of a single metabolic enzyme cannot solely describe the risk of breast cancer. In addition, to confirm the association observed in the present study, a systematic approach taking account of potentially relating polymorphisms is desirable in the near future.

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References
1. Henderson BE, Feigelson HS: Hormonal carcinogenesis. Carcinogenesis 2000, 21:427-433.
2. Stoll BA, Secreto G: New hormone-related markers of high risk to breast cancer. Ann Oncol 1992, 3:435-438.
3. Buda B, Szamel I, Sulyok Z, Nemet M, Bak M, Otto S, Reed MJ, Purohit A, Parish DC, Krilovanszky J: Characteristics of cystic breast disease with special regard to breast cancer development. Anticancer Res 2001, 21:749-752.
4. Dorgan JF, Longcope C, Stephens HN, Car Breast cancer risk. Cancer Epidemiol Biomarkers Prev 1996, 5: 533-539.
5. Berrino F, Miti P, Michelini A, Bolelli G, Krogh V, Sciajno R, Pisani P, Panico S, Secreto G: Serum sex hormone levels after menopause and subsequent breast cancer. J Natl Cancer Inst 1996, 88:291-296.
6. Cauley JA, Lucas FL, Koller LH, Stone K, Browner W, Cummings SR: Elevated serum estradiol and testosterone concentrations are associated with a high risk for breast cancer. Ann Intern Med 1999, 130:270-277.
7. Lapointe J, Labrie C: Role of the cyclin-dependent kinase inhibitor p27Kip1 in androgen-induced inhibition of CAMA-1 breast cancer cell proliferation. Endocrinology 2001, 142: 4331-4338.
8. Dauvois S, Geng CS, Levesque C, Merad Y, Labrie F: Additive inhibitory effects of an androgen and the antiestrogen EM-170 on estradiol-stimulated growth of human ZR-75-1 breast tumors in athymic mice. Cancer Res 1991, 51:3131-3135.
9. Labrie F, Simard J, de Launoit Y, Poulin R, Theriault C, Dumont M, Dauvois S, Martel G, Li SM: Androgens and breast cancer. Cancer Detect Prev 1992, 16:31-38.
10. Ingle JN, Twito DI, Schaid DJ, Cullinan SA, Krook JE, Mailliard JA, Tschetter LK, Long HJ, Gerstner JG, Windschitl HE: Combination hormonal therapy with tamoxifen plus fluoroxymesterone versus tamoxifen alone in postmenopausal women with...
metastatic breast cancer. An updated analysis. Cancer 1991, 67:886-891.

11. Suzuki T, Darnel AD, Akahira JI, Ariga N, Ogawa S, Kaneko C, Takeyama J, Moriya T, Sasoano H: 5α-reductases in human breast carcinoma: possible modulator of in situ androgenic actions. J Clin Endocrinol Metab 2001, 86:2250-2257.

12. Labrie F, Sugimoto Y, Luu-The V, Simard J, Lachance Y, Bachvarov D, Leblanc G, Durocher F, Paquet N: Structure of human type II 5α-reductase gene. Endocrinology 1992, 131:1571-1573.

13. Vichis F, Mendez JP, Canto P, Lieberman E, Chavez B: Identification of missense mutations in the SRD5A2 gene from patients with steroid 5α-reductase 2 deficiency. Clin Endocrinol 2000, 52:383-387.

14. Makridakis N, Ross RK, Pike MC, Chang L, Stanczyk FZ, Kolonel LN: A prevalent missense substitution that modulates activity of prostatic steroid 5α-reductase. Cancer Res 1997, 57:1020-1022.

15. Allen NE, Forrest MS, Key TJ: The association between polymorphisms in the CYP17 and 5α-reductase (SRD5A2) genes and serum androgen concentrations in men. Cancer Epidemiol Biomarkers Prev 2001, 10:185-189.

16. Reichardt JK, Makridakis N, Henderson BE, Yu MC, Pike MC, Ross RK: Genetic variability of the human SRD5A1 gene: implication for prostate cancer risk. Cancer Res 1995, 55:3973-3975.

17. Hsing AW, Chen C, Chokkalingam AP, Gao YT, Dightman DA, Nguyen HT, Deng J, Cheng J, Sesterhenn IA, Mostofi FK, Stanczyk FZ, Reichardt JK: Polymorphic markers in the SRD5A2 gene and prostate cancer risk: a population-based case–control study. Cancer Epidemiol Biomarkers Prev 2001, 10:1077-1082.

18. Makridakis NM, Ross RK, Pike MC, Crocitto LE, Kolone LN, Pearce CL, Henderson BE, Reichardt JK: Association of missense substitution in SRD5A2 gene with prostate cancer in African-American and Hispanic men in Los Angeles, USA. Lancet 1999, 354:975-978.

19. Bharaj B, Scornilas A, Giai M, Diamandis EP: TA repeat polymorphism of the 5α-reductase gene and breast cancer. Cancer Epidemiol Biomarkers Prev 2000, 9:387-393.

20. Kantoff PW, Febbo PG, Giovannucci E, Khthivas K, Dahl DM, Chang G, Hennekens CH, Brown M, Stamper MJ: A polymorphism of the 5 α-reductase gene and its association with prostate cancer: a case–control analysis. Cancer Epidemiol Biomarkers Prev 1997, 6:189-192.

21. Febbo PG, Kantoff PW, Platz EA, Casey D, Bant T, Giovannucci E, Hennekens CH, Stamper MJ: The V89L polymorphism in the 5α-reductase type 2 gene and risk of prostate cancer. Cancer Res 1999, 59:5878-5881.

22. Margiotti K, Sangiulio F, De Luca A, Froio F, Pearce CL, Ricci-Barbini V, Micali F, Bonafe M, Franceschi C, Dallapiccola B, Novelli G, Reichardt JK: Evidence for an association between the SRD5A2 (type II steroid 5α-reductase) locus and prostate cancer in Italian patients. Dis Markers 2000, 16:147-150.

23. Latil AG, Azzouzi R, Cancel GS, Guillaume EC, Cochon-Prielot B, Berthon PL, Cussenet O: Prostate carcinoma risk and allelic variants of genes involved in androgen biosynthesis and metabolism pathways. Cancer 2001, 92:1130-1137.

24. Yamada Y, Watanabe M, Murata M, Yamanaka M, Kubota Y, Ito H, Kato H, Kawamura J, Yatani R, Shiraiishi T: Impact of genetic polymorphisms of 17-hydroxylase cytochrome P-450 (CYP17) and steroid 5α-reductase type II (SRD5A1) genes on prostate-cancer risk among the Japanese population. Int J Cancer 2001, 92:683-686.

25. Narn RK, Toi A, Vesprini D, Ho M, Chu W, Harvie S, Sweet J, Traechtenberg J, Jewett MA, Narod SA: V89L polymorphism of type-2, 5α-reductase, enzyme gene predicts prostate cancer presence and progression. Urology 2001, 57:199-204.

26. Mononen N, Ikonen T, Syrjakoski K, Matkainen M, Schleutker J, Tammela TLJ, Koivisto PA, Kallioniemi OP: A missense substitution A49T in the steroid 5α-reductase gene (SRD5A2) is not associated with prostate cancer in Finland. Br J Cancer 2001, 84:1344-1347.

27. Scornilas A, Bharaj B, Giai M, Diamandis EP: Codon 89 polymorphisms in the human 5α-reductase gene in primary breast cancer. Br J Cancer 2001, 84:760-767.