The Steroid 5α-Reductase Type II TA Repeat Polymorphism Is Not Associated with Risk of Breast or Ovarian Cancer in Australian Women

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Abstract

The enzyme 5α-reductase type II (SRD5A2) converts testosterone to its more active form 5α-dihydroxytestosterone. The 3′ untranslated region of the gene contains a (TA)n length polymorphism. The (TA)n allele has been reported to be associated with higher serum prostate-specific antigen levels in breast tumors and lower risk of relapse in breast cancer patients and more recently has also been reported to be linked to the codon 89 valine variant, which is itself associated with higher serum prostate-specific antigen levels in breast tumors and a more favorable breast cancer prognosis.

We investigated whether the SRD5A2 (TA)n polymorphism was associated with risk of breast or ovarian cancer in Australian women by studying 946 breast cancer cases and 509 age-matched controls, and 544 ovarian cancer cases and 298 controls of similar age distribution. The (TA)n allele frequency was similar in breast cancer cases (0.110), breast cancer controls (0.125), ovarian cancer cases (0.106), and ovarian cancer controls (0.117). There was no difference in genotype distribution between breast cancer cases and controls (P = 0.5), ovarian cancer cases and controls (P = 0.7), or between the two control groups (P = 0.9). Genotypes containing at least one (TA)n allele were not significantly associated with risk of breast cancer overall (odds ratio, 0.86; 95% confidence interval, 0.67–1.12; P = 0.3) or in women stratified by age, menopausal status, or family history. Similarly, the (TA)n allele was not associated with risk of ovarian cancer (odds ratio, 0.87; 95% confidence interval, 0.61–1.23; P = 0.4) or with ovarian tumor behavior (invasive or low malignant potential), histology, stage, or grade. Given that this study had sufficient power to detect altered risks in the order of 1.4- to 1.7-fold, our results suggest that the SRD5A2 (TA)n allele is unlikely to be associated with moderate alterations in breast or ovarian cancer risk.

Introduction

“High-risk” mutations in the tumor suppressor genes BRCA1 and BRCA2 and mismatch repair genes hMSH2 and hMLH1 are responsible for only a small proportion of breast and ovarian cancers in the population (1, 2). Common allelic variants that slightly alter the usual function of these or other genes may act as “low-risk” variants, and as such could account for a greater proportion of both sporadic and familial cancers. Because endogenous and exogenous steroid hormone exposure is considered to alter the risk of breast and ovarian cancer (3–6), there is currently interest in the association between common genetic variants in hormone biosynthesis genes and susceptibility to breast and ovarian cancer (7).

The enzyme 5α-reductase type II (SRD5A2) converts testosterone to the more active form 5α-dihydroxytestosterone, which binds to the androgen receptor to form the active hormone-receptor complex capable of nuclear gene transactivation. The 3′ untranslated region of the gene contains a (TA)n length polymorphism caused by the insertion of 9 or 18 TA dinucleotides and other alterations in the nearby gene sequence (8). The (TA)n allele is most common, and the (TA)9 and (TA)18 allele frequencies were initially reported to be 0.02 and 0.01, respectively, in a sample of 172 chromosomes from individuals of undisclosed ethnicity (8). A subsequent study of non-Hispanic whites (n = 68), Asian Americans (n = 37) and African Americans (n = 94) showed that, under high resolution electrophoresis, the (TA)n allele appeared to comprise a single core allele and a few minor variants differing by a few base pairs from the core allele, whereas the (TA)18 allele included six rare variants ranging in size by 10 bp overall (9). The (TA)n variants had a frequency of 7–11% across the three population groups, and the larger (TA)18 variants were observed

1 The abbreviations used are: SRD5A2, 5α-reductase type II; AR, androgen receptor; CL, confidence interval; OR, odds ratio; PSA, prostate-specific antigen.
in the African American sample only at a frequency of 9% (9). Given that such differences in genotype distribution mirror racial differences in SRD5A2 serum activity and prostate cancer incidence, i.e., increased activity and cancer incidence in African Americans, these authors proposed that the SRD5A2 (TA)18 allele may be associated with prostate cancer risk (9). Pilot data based on samples of <60 men/group appeared to support an association of prostate cancer risk with (TA)18 in African Americans and (TA)9 in white Americans (9). However, a more comprehensive study of 509 prostate cancer cases and 802 controls found no association between risk of prostate cancer and the (TA)9 or (TA)18 alleles, although there was a suggestion that homozygotes for the (TA)9 and (TA)18 alleles may be underrepresented among cases (10).

This SRD5A2 length polymorphism was investigated recently for its association with breast cancer risk and clinicopathological variables in a sample of 70 normal female controls and 141 breast cancer cases, using DNA extracted from tumors of cases (11). There was no difference in genotype distribution between cases and controls; however, cases carrying at least one (TA)9 allele showed a reduction in risk of relapse (P = 0.04; Ref. 11). Furthermore, genotypes with at least one (TA)9 allele were associated with increased serum PSA levels in the breast tumors (P = 0.004; Ref. 11). Because the 5α-dihydroxytestosterone-AR complex transactivates the PSA gene, the results were interpreted to suggest that longer TA repeat alleles may be associated with upregulated SRD5A2 activity in breast tumors. Furthermore, a more recent study by the same research group (12) showed that the TA polymorphism is in linkage disequilibrium with the SRD5A2 Val89Leu polymorphism, and that the (TA)9 allele appears to be linked to the Val variant, which is in turn associated with increased serum PSA levels in the breast tumors and more favorable breast cancer prognosis. As such, the SRD5A2 (TA)9 allele could be considered a candidate marker for low-risk genetic predisposition to hormonally related breast and ovarian cancers.

To examine whether the SRD5A2 (TA)9 polymorphism is associated with breast or ovarian cancer risk, we have undertaken large case-control studies of these cancers in the Australian population.

Subjects and Methods

Population-based Breast Cancer Cases and Controls. A population-based case-control-family study of early-onset breast cancer in women <40 years of age was carried out in Melbourne and Sydney from 1992 to 1995 (13, 14) and was continued and extended to include women up to 59 years of age from 1996 to 2000 (15). Cases were women with a diagnosis of a first primary breast cancer in a sample of 70 normal female controls and 141 breast cancer cases. Genotyped cases ranged in age at diagnosis from 23 to 59 years (average, 41.1 years; SD, 8.6) and were grouped by age at diagnosis as follows: <40 (n = 545; 57.6%), 40–49 (n = 198; 20.9%), and 50–59 (n = 203; 21.5%) years. Menopausal status was recorded for 921 cases (97.4%) and 737 (80.0%) of these individuals were premenopausal. Family history of breast cancer in first- or second-degree relatives was reported by 319 (33.7%) of genotyped cases. Genotyped controls ranged in age at interview from 20 to 59 years (average, 39.2 years; SD, 8.0) and were grouped by age at diagnosis as follows: <40 (n = 344; 67.6%), 40–49 (n = 91; 17.9%), and 50–59 (n = 74; 14.5%) years. Menopausal status was recorded for 498 controls (97.8%), and 420 (84.3%) of these individuals were premenopausal. Family history of breast cancer in first- or second-degree relatives was reported by 120 (23.6%) of genotyped controls.

To date, 30 case subjects included in the SRD5A2 analysis have been found to have a deleterious mutation in either BRCA1 or BRCA2 by protein-truncation testing in specific exons covering ~70% of the coding regions and manual sequencing of BRCA1 and BRCA2 in a subset (16, 17). Mutation testing in these samples is ongoing, and thus far has been carried out on 542 of genotyped cases, all of whom were <40 years at diagnosis.

Ovarian Cancer Cases and Controls. Cases with epithelial ovarian adenocarcinoma (n = 556) were ascertained as incident cases from several sources: the Royal Brisbane Hospital, Queensland, Australia, during the period 1985–1996 (n = 190); major gynecological-oncology treatment centers in New South Wales, Victoria and Queensland as part of a large
population-based case-control study (18) \((n = 241)\); or from both sources \((n = 125)\). The age at diagnosis of cases ranged from 19 to 95 years, with an average of 57.4 years (SD, 13.6). Age at diagnosis was distributed as follows: 0–9 \((n = 56; 10\%)\), 10–19 \((n = 100; 18\%)\), 20–29 \((n = 140; 25\%)\), 30–39 \((n = 149; 27\%)\), and 40–69 \((n = 111; 20\%)\) years. Histopathological information available for these cases included tumor behavior (low malignant potential or invasive), histology, stage, and grade. The series comprised 97 (17\%) low malignant potential and 459 (83\%) invasive tumors. There were 329 (59\%) serous, 69 (12\%) mucinous, 64 (12\%) endometrioid, 32 (6\%) clear cell carcinoma, 12 (2\%) mixed Mullerian, 25 (5\%) mixed, and 17 (3\%) undifferentiated tumors, as well as 8 (1\%) of unknown histology. For analysis with respect to histology, the mixed Mullerian and mixed histologies were treated as a single mixed group. Patients were staged at laparotomy in accordance with the recommendations of the International Federation of Gynecology and Obstetrics (19). Of the 426 invasive tumors of known stage, there were 77 (18\%), 49 (11\%), 292 (69\%) stage 1, 48 (11\%), 259 (61\%), and 42 (10\%) at International Federation of Gynecology and Obstetrics stages 1, 2, 3, and 4, respectively. Grade definitions were drawn directly from pathology reports for 393 of the invasive tumors and comprised 52 (13\%) grade 1, 8 (2\%) grade 1/2, 107 (27\%) grade 2, 56 (14\%) grade 2/3, 163 (42\%) grade 3, 1 (<1\%) grade 3/4, and 5 (1\%) grade 4 tumors. The grades 1/2, 2/3, and 3/4 reflected grades considered indistinguishable by the pathologists. For analysis of trends in grade with genotype frequency, tumors of grade 1/2 were excluded because of the small sample size of this group, whereas the high grades 3, 3/4, and 4 were treated as single group of grade 3–4.

Information on potential or known ovarian cancer risk factors was collected at interview as part of the population-based case-control study and was available for 366 (66\%) cases. The sample included 82 (22\%) nulliparous women, 226 (62\%) women with 1–3 liveborn children, and 58 (16\%) women with 4 or more liveborn children. Other variables included in analysis were oral contraceptive use [181 (50\%) ever, 185 (50\%) never] and tubal ligation [42 (12\%) ever, 324 (88\%) never]. SRD5A2 genotyping was performed on the 548 cases for whom DNA was available at the time of genetic analysis. SRD5A2 genotype results were obtained for 544 ovarian cancer cases (97.8\% of cases ascertained for molecular studies), constituting a PCR success rate of 99\%. Ovarian cancer cases with genotype information did not differ significantly from the total sample with respect to tumor characteristics, age, or other measured risk factors listed above \((P \geq 0.9\) for all comparisons).

Tissue samples for DNA extraction were not collected from the controls included in the original ovarian cancer case-control study (18), and it was therefore not possible to use these population-based controls for genetic analysis. Control individuals from another source were thus used for SRD5A2 genotype analysis, as described previously (20). Briefly, 300 unrelated adult female monozygotic twins (one per pair) were selected from a sample of 3348 twins recruited through the volunteer national Australian Twin Registry for the Semi Structured Assessment for the Genetics of Alcoholism research study (21). Similar to cases, controls were of almost exclusively European descent and were recruited from major cities in the eastern states of Australia (21). Controls were selected by date of birth to best match the date-of-birth distribution of cases, i.e., one-third from each of 1900–1925, 1926–1938, and 1939–1970. Age at interview ranged from 30 to 90 years, with an average of 50.9 years (SD, 13.9) and was distributed as follows: <40 \((n = 85; 28\%)\), 40–49 \((n = 61; 20\%)\), 50–59 \((n = 65; 22\%)\), 60–69 \((n = 56; 19\%)\), and 70–79 \((n = 33; 11\%)\) years. Limited information on potential or known risk factors for ovarian cancer was available from controls. Parity data collected at interview was available for 294 (98\%) controls, and the sample included 38 (13\%) nulliparous women, 171 (58\%) women with 1–3 liveborn children, and 79 (29\%) women with 4 or more liveborn children. No additional epidemiological information was available from controls to adjust for possible confounding. SRD5A2 genotyping was carried out on the 300 controls described above. SRD5A2 genotype results were obtained for 298 controls (99\% of the sample ascertained as controls for ovarian cancer molecular studies). Controls with genotype information did not differ from the total sample with respect to age or parity \((P = 1.0\) for both comparisons).

Approval of the breast cancer case-control-family study protocol was obtained from the ethics committees of The University of Melbourne, the New South Wales Cancer Council, the Anti-Cancer Council of Victoria, and The Queensland Institute of Medical Research. Ethical clearance for collection of subject information and blood from ovarian cancer cases and controls was given by the Queensland Institute of Medical Research Ethics Committee.

### Molecular Analysis

Collection of germ-line tissue and DNA extraction for cancer cases and controls has been described previously (20, 22, 23). Of the total ovarian cancer samples genotyped, DNA was extracted from archival blocks of germ-line tissue for 259 of the ovarian cancer cases ascertained though the population-based case-control study (47.6\% of the total ovarian sample). The SRD5A2 \((TA)_n\) insertion length polymorphism (8) was detected by PCR, followed by high resolution agarose gel electrophoresis. The product was ampli-
Fig. 1. Frequency of SRD5A2 (TA)9/(TA)9 and (TA)9/(TA)9 genotypes, pooled, in cases and controls. The 95% CI of the genotype frequency is indicated by a black line for each column. Shaded columns, cases; white columns, controls. A, frequency of genotypes containing at least one (TA)9 allele in the unstratified samples of breast cancer cases, breast cancer controls, ovarian cancer cases, and ovarian cancer controls. B, frequency of genotypes containing at least one (TA)9 allele in breast cancer cases and controls stratified by age at onset (<40 or >40 years), family history of breast cancer reported in first- or second-degree relatives, menopausal status, and in subjects of Caucasian ancestry. C, frequency of genotypes containing at least one (TA)9 allele in ovarian cancer cases stratified by tumor behavior, histology, stage, and grade. LMP, low malignant potential; BN, invasive; SER, serous; MUC, mucinous; END, endometrioid; CCC, clear cell carcinoma; MXD, mixed.
fied using the forward primer AGCTCCCACAATGCTGAGAA and the reverse primer AGCAGACACCACTCAGAATCCC. The 10-μl reaction mix contained 30 ng of DNA, primers (200 nM each), deoxyribonucleotide triphosphates (200 nM), 1× Perkin-Elmer Taq polymerase buffer, 1 unit of Taq polymerase, and 1.5 mM MgCl₂. Amplifications were incubated for 4 min at 94°C, 4 cycles at 94°C for 20 s, 67°C for 20 s, and 72°C for 20 s; 4 cycles at 94°C for 20 s, 65°C for 20 s, and 72°C for 20 s; and 26 cycles at 94°C for 20 s, 63°C for 20 s, and 72°C for 20 s, followed by a 10-min extension at 72°C. Reaction products were resolved on 4.5% Nusieve gels and were sized relative to a 20-bp ladder (Bio-Rad) run in a separate lane on each row of the same gel. The approximate band sizes for the (TA)₀ and (TA)₉ alleles were 135 and 153 bp, respectively, and the expected band size for the (TA)₁₈ allele was 171 bp.

**Statistical Methods.** Allele frequencies were estimated and compared by assuming that alleles within an individual are independent binary variables. The SRD5A2 (TA)₀/(TA)₀ and (TA)₀/(TA)₀ genotypes were pooled in some subsequent analyses because of the rarity of the allele. Deviations from Hardy-Weinberg equilibrium were assessed by the standard goodness-of-fit test based on likelihood theory as described by Spurdle et al. (24). The Pearson goodness-of-fit test was used to assess differences in SRD5A2 (TA)₀ genotype prevalence among ovarian cancer cases with respect to age, oral contraceptive use, and tubal ligation, and among ovarian cancer controls with respect to age and parity. Student’s t test was used to compare the mean ages at diagnosis of cases with the mean age at interview of controls. The association between SRD5A2 genotype and risk of breast or ovarian cancer was assessed, as in standard case-control analyses, by unconditional linear logistic regression, with and without adjustment for measured risk factors.

All statistical tests and Ps were two-tailed and, following convention, statistical significance was taken as a nominal P of <0.05. SPSS (version 9.0) and Ottutil software were used for statistical analyses.

**Results**

The (TA)₁₈ allele was not observed in this study. The frequency (95% CI) of the SRD5A2 (TA)₀ allele in breast cancer cases, breast cancer controls, ovarian cancer cases, and ovarian cancer controls was 0.110 (0.096–0.124), 0.125 (0.104–0.145), 0.106 (0.087–0.124), and 0.117 (0.092–0.143), respectively (Table 1). There was no difference in allele frequency between breast cancer cases and controls with respect to age, reported first- or second-degree family history of breast cancer, country of birth (Australia versus elsewhere), education level, marital status, parity, height, weight, age at menarche, and oral contraceptive use (see Ref. 14 for details on the categorization of these variables). Similarly, logistic regression was used to assess differences in SRD5A2 (TA)₀ genotype prevalence among ovarian cancer cases with respect to age, oral contraceptive use, and tubal ligation, and among ovarian cancer controls with respect to age and parity. Student’s t test was used to compare the mean ages at diagnosis of cases with the mean age at interview of controls. The association between SRD5A2 genotype and risk of breast or ovarian cancer was assessed, as in standard case-control analyses, by unconditional linear logistic regression, with and without adjustment for measured risk factors.

All statistical tests and Ps were two-tailed and, following convention, statistical significance was taken as a nominal P of <0.05. SPSS (version 9.0) and Ottutil software were used for statistical analyses.
groups ($P = 0.4, 0.4, 0.2, \text{and} 0.6$, respectively). The genotype distribution did not differ between breast cancer cases and controls ($P = 0.5$), between ovarian cancer cases and controls ($P = 0.7$), or between the two control groups ($P = 0.9$). There was also no difference in genotype distribution between ovarian cancer cases with DNA extracted from blood, compared with those with DNA extracted from archival blocks ($P = 0.9$), i.e., there was no apparent effect of DNA quality on genotype results.

The (TA)$_b$/TA$_b$ genotype was rare ($\leq 2\%$ frequency in the four groups) and did not differ in frequency between breast cancer cases and controls ($P = 0.5$) or between ovarian cancer cases and controls ($P = 0.8$). The (TA)$_a$/TA$_b$ and (TA)$_b$/TA$_b$ genotypes were thus pooled for further analysis.

Fig. 1 shows the prevalence of the pooled (TA)$_a$/TA$_b$ and (TA)$_b$/TA$_b$ genotypes in cases and controls. As shown in Fig. 1A, the prevalence of the genotype containing at least one (TA)$_a$ allele ranged from 19.5% in ovarian cancer cases to 23.0% in breast cancer controls, but the 95% CIs for all frequencies overlapped considerably. There was no difference in the prevalence of this genotype between breast cancer cases and controls ($P = 0.3$), between ovarian cancer cases and controls ($P = 0.4$), or between the two control groups ($P = 0.7$). There was also no difference in prevalence between breast cancer cases and controls stratified (Fig. 1B) by age $\leq 40$ or $>40$ years ($P = 0.2$ and 0.6, respectively), by reported first- or second-degree family history of breast cancer ($P = 0.9$ and 0.2 for those with and without a family history, respectively), by menopausal status ($P = 0.2$ and 0.9 for premenopausal and postmenopausal subjects, respectively), or when analyses were limited to Caucasian subjects only ($P = 0.4$). For ovarian cancer cases (Fig. 1C), there was no difference in genotype prevalence across subgroups defined by ovarian tumor behavior (LMP versus invasive; $P = 0.8$), histology ($P = 0.7$), stage ($P = 0.4$), or grade ($P = 0.2$).

The prevalence of the SRD5A2 (TA)$_b$ variant did not vary with age at onset across ovarian cancer cases ($P = 0.6$) or age at interview for ovarian cancer controls ($P = 0.3$). Although there was a suggestion of a trend of decreasing prevalence with increasing age in both breast cancer cases ($P = 0.1$) and breast cancer controls ($P = 0.06$), there was no difference between cases and controls in the magnitude of this trend ($P_{\text{interaction}} = 0.5$). The genotype prevalence did not vary within breast cancer cases or controls with any of the other measured variables used in the risk analyses below ($P \geq 0.1$) or within the ovarian cancer cases with the possible confounders parity ($P = 0.8$) and tubal ligation ($P = 0.9$), or within ovarian cancer controls with parity ($P = 0.1$).

The associations between the pooled SRD5A2 (TA)$_b$ genotype and risk of breast and ovarian cancer, as assessed by case-control analyses, are presented in Table 2. There was no evidence that the SRD5A2 (TA)$_b$ variant was associated with risk of breast or ovarian cancer, before or after adjustment for established risk factors or potential confounders. Overall findings were unchanged for analysis of breast cancer risk after stratification, as shown in Fig. 1B ($<40$ only, $>40$ only, family history-positive, family history-negative, premenopausal, postmenopausal, and Caucasian only). For example, the adjusted OR ($95\%$ CI) for women $<40$ years was 0.76 (0.55–1.06; $P = 0.1$), whereas the adjusted OR for women with a family history was 0.94 (0.54–1.64; $P = 0.8$). Similarly, there was no indication that the SRD5A2 (TA)$_b$ variant was associated with risk of ovarian cancer when restricted to the larger subgroups of invasive or serous cancers. The age-adjusted ORs ($95\%$ CI) were 0.80 (0.54–1.16; $P = 0.2$) and 0.95 (0.64–1.41; $P = 0.8$) for invasive and serous cancers, respectively. In addition, results were no different for analysis of a subsample of ovarian cancer cases for which it was possible to make adjustment for both age and parity [OR ($95\%$ CI), 0.95 (0.65–1.41); $P = 0.8$]. Because there was no difference in pooled genotype prevalence or overall genotype distribution between breast cancer controls and ovarian cancer controls ($P \geq 0.8$), ovarian cancer cases were also compared with breast controls. Overall findings were no different for both crude and age-adjusted ORs.

### Discussion

The frequency of the (TA)$_b$ allele in Australian female controls (0.12–0.13) was similar to that reported for a large sample ($n = 802$) of North American male controls of largely Caucasian origin (0.13; Ref. 10). In addition, we did not observe the (TA)$_a$ allele in our largely Caucasian sample, supporting published evidence that this allele is absent or extremely rare in Caucasian populations (9). There was no difference between cases and controls in the distribution of (TA) genotypes and more specifically in the frequency of the (TA)$_a$/TA$_b$ or pooled (TA)$_b$/TA$_b$ genotype prevalence. Overall, there was no indication that the (TA)$_b$ variant was associated with a significantly altered risk of breast cancer or ovarian cancer. There was also no evidence to suggest that the (TA)$_b$ variant was associated with breast cancer for specific subgroups of women or with specific subtypes of ovarian cancer.

To our knowledge, there are no published investigations of the association between the SRD5A2 TA repeat polymorphism and ovarian cancer risk and only one published study that has investigated the association between this polymorphism and breast cancer risk (11). The latter study showed no significant difference in genotype distribution in a relatively small sample of 141 breast tumors and 70 controls. However, patients with heterozygote and homozygote (TA)$_b$ genotypes presented with lower stage of disease and had a reduced risk of relapse (11). A more recent study by the same research group (12) showed that
the (TA)_9 allele appears to be linked to the codon 89 Val variant, which is itself associated with more favorable breast cancer prognosis. In light of these reported associations with breast cancer clinicopathological variables (11, 12), it is interesting to note that the (TA)_9 allele frequency is lower in cancer cases compared with controls, and that risk estimates observed in this study for (TA)_9-containing genotypes were below zero for both breast cancer and ovarian cancer. Although this suggests that the (TA)_9 allele may be associated with a protective effect, possibly as a result of linkage disequilibrium with the codon 89 Val allele, such an effect is unlikely to be of moderate magnitude. This study had 80% power at the 0.05 level of significance to detect an OR of 0.7 (equivalent to an increased risk of 1.4) for the breast cancer case-control comparison and the same power to detect an OR of 0.6 (equivalent to an increased risk of 1.6) for the ovarian cancer case-control comparison. However, we cannot exclude the possibility of small effects on breast or ovarian cancer risk. There are currently no data with respect to the functional significance of the (TA)_9 and Val89Leu polymorphisms with respect to SRD5A2 mRNA stability and/or protein expression. Given the linkage disequilibrium observed between the two variants, such an investigation would be essential to shed light on whether either or both of these variants have relevance with respect to SRD5A2 activity in vivo and thus pinpoint future directions of research.

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References


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