

*Short Communication*

## Sources of Elevated Serum Androgens in Postmenopausal Women Who Develop Breast Cancer

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**Abstract**

**Postmenopausal women with elevated serum androgens are at an increased risk of breast cancer. High dehydroepiandrosterone sulfate concentrations in these women suggest increased adrenal secretion. Both the adrenals and ovaries could contribute to elevated concentrations of androstenedione ( $\Delta^4\text{A}$ ).  $11\beta$ -Hydroxyandrostenedione ( $11\beta\text{OHA}$ ) is elevated, and the  $\Delta^4\text{A}:11\beta\text{OHA}$  ratio is depressed when the adrenals are the primary source of elevated  $\Delta^4\text{A}$  in women. Conversely,  $\Delta^4\text{A}:11\beta\text{OHA}$  is elevated when the ovaries are the primary source. We prospectively evaluated associations of serum  $11\beta\text{OHA}$  and  $\Delta^4\text{A}:11\beta\text{OHA}$  with breast cancer in the Columbia, Missouri Serum Bank to identify the source of elevated  $\Delta^4\text{A}$  related to risk. Fifty-three postmenopausal women who were not taking estrogens when they donated blood and were diagnosed with breast cancer up to 10 years later (median, 2.9 years) served as cases. Two controls, who were also postmenopausal and not taking estrogens, were matched to each case on age, date, and time of blood collection. Serum  $\Delta^4\text{A}$  concentration was significantly (trend  $P = 0.02$ ) positively associated with breast cancer risk. Adjusted risk ratios for women in the lowest to highest tertiles were 1.0, 1.6, and 2.4 [95% confidence interval (CI), 0.9–6.5]. However, neither  $11\beta\text{OHA}$  concentration nor  $\Delta^4\text{A}:11\beta\text{OHA}$  was related to risk. Comparable risk ratios were 1.0, 1.2, and 1.4 (95% CI, 0.5–3.6) for  $11\beta\text{OHA}$  and 1.0, 1.2, and 1.2 (95% CI, 0.4–3.5) for  $\Delta^4\text{A}:11\beta\text{OHA}$ . Our results suggest that neither the ovaries nor adrenals are the predominant source of elevated serum**

**$\Delta^4\text{A}$  in postmenopausal women who develop breast cancer, but rather both may contribute.**

**Introduction**

Postmenopausal women with elevated serum concentrations of DHEA<sup>2</sup>, DHEAS,  $\Delta^4\text{A}$ , and testosterone have been reported to be at an increased risk of breast cancer in several cohort studies (1–7). Elevated DHEA and DHEAS serum concentrations in women who develop breast cancer suggest increased adrenal androgen secretion (8). The source of excess  $\Delta^4\text{A}$  and testosterone is less clear. Raised serum  $\Delta^4\text{A}$  concentrations could be the consequence of increased secretion by the adrenals or ovaries or increased peripheral conversion of DHEA, whereas elevated testosterone levels are more likely attributable to increased ovarian secretion or peripheral conversion of  $\Delta^4\text{A}$  and, to a lesser extent, DHEA (8–10).

$11\beta\text{OHA}$  is an inactive metabolite of  $\Delta^4\text{A}$  and cortisol that is synthesized predominantly by the adrenals and is used as a serological marker to identify the source of elevated serum androgens in women (11–14). The  $\Delta^4\text{A}:11\beta\text{OHA}$  ratio in serum is a better discriminator than the concentration of  $11\beta\text{OHA}$  alone (15). Serum levels of  $11\beta\text{OHA}$  are elevated, and the  $\Delta^4\text{A}:11\beta\text{OHA}$  ratio is depressed when the adrenals are the primary source of elevated serum androgens. Conversely, when the ovaries are the primary source of circulating androgens, the concentration of  $11\beta\text{OHA}$  is unchanged, but the  $\Delta^4\text{A}:11\beta\text{OHA}$  ratio is elevated.

In previous reports (1, 2) from the Columbia, Missouri Serum Bank, we showed that prediagnostic serum concentrations of DHEA, DHEAS,  $\Delta^4\text{A}$ , and testosterone were significantly elevated in postmenopausal women who subsequently were diagnosed with breast cancer. The current manuscript reports findings on the relationships of serum  $11\beta\text{OHA}$  and  $\Delta^4\text{A}:11\beta\text{OHA}$  with risk in these women.

**Materials and Methods**

The current study is an extension of our previous studies on the relationships of serum sex hormones to breast cancer risk based on the Columbia, Missouri Serum Bank. This serum bank includes serum from 7224 cancer-free volunteers identified primarily through the Breast Cancer Detection Demonstration Project at the Ellis Fischel Cancer Center and University of Missouri Hospital in Columbia. Details about the serum bank participants, data collection, and serum collection and storage have been described previously (1, 2).

To be eligible for inclusion in the nested case-control studies of hormones and breast cancer, women had to be postmenopausal, not taking replacement estrogens at the time of

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<sup>2</sup> The abbreviations used are: DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate;  $\Delta^4\text{A}$ , androstenedione;  $11\beta\text{OHA}$ ,  $11\beta$ -hydroxyandrostenedione; RR, risk ratio; BMI, body mass index; CI, confidence interval.

Table 1 Characteristics (mean  $\pm$  SE) of cases and controls at blood collection

	Cases (n = 53)	Controls (n = 106)	P <sup>a</sup>
Age at blood collection (yr)	61.8 $\pm$ 0.9	61.9 $\pm$ 0.6	0.87
Age at menopause (yr)	49.3 $\pm$ 0.5	49.1 $\pm$ 0.5	0.81
Age at menarche (yr)	13.0 $\pm$ 0.2	12.8 $\pm$ 0.1	0.46
Parity	2.1 $\pm$ 0.2	2.5 $\pm$ 0.2	0.25
Age at first pregnancy (yr) <sup>b</sup>	22.7 $\pm$ 0.5	24.0 $\pm$ 0.4	0.11
Height (cm)	162.2 $\pm$ 0.8	161.0 $\pm$ 0.5	0.09
Weight (kg)	70.3 $\pm$ 1.6	68.9 $\pm$ 1.3	0.36
BMI (kg/m <sup>2</sup> )	26.7 $\pm$ 0.5	26.6 $\pm$ 0.5	0.46

<sup>a</sup> P from Wilcoxon rank-sum test (2-sided).

<sup>b</sup> Parous participants (n = 40 cases, 87 controls).

blood collection, and have no history of cancer other than nonmelanoma skin cancer. Of the 3375 women who met these criteria, 71 subsequently were diagnosed with histologically confirmed breast cancer and were included in our previous analyses. Fifty-three of these 71 cases had a sufficient volume of prediagnostic serum remaining in the serum bank to be included in the current analysis. Many women donated blood to the serum bank on multiple occasions, and serum from each collection was separated into 1-ml aliquots. An aliquot from the same blood collection time used for other hormone measurements was still available for 43 of the cases included in the current analysis. For the remaining 10 cases, an aliquot from a different blood collection time was used.

For each case, two controls were selected from among the eligible women using incidence density sampling. Whenever possible, the same controls were used as in our earlier studies. New controls were identified for the 10 cases whose serum was from a different blood draw than previously. An additional 11 new controls were needed because serum was no longer available for the controls used previously. Controls were alive and free of cancer (except nonmelanoma skin cancer) at the age of the case's diagnosis and were matched to the case on the exact age at blood collection and on the date ( $\pm$ 1 year) and time ( $\pm$ 2 h) of the blood draw. To identify controls for three cases, matching criteria were relaxed as follows: (a) age  $\pm$  1 year (n = 1); (b) age  $\pm$  4 years, blood draw  $\pm$  2 years, and  $\pm$  4 h (n = 1); and (c) age  $\pm$  1 year, blood draw  $\pm$  9 h (n = 1).

Serum was stored at  $-70^{\circ}\text{C}$  for a median of 19 years before analysis for both cases and controls. None of the samples were thawed before being shipped to laboratories for analysis. Serum samples from each case and her matched controls were grouped and analyzed together in the same batch. 11 $\beta$ OH was extracted with cyclohexane:ethyl acetate (1:1), chromatographed on Celite impregnated with diethylene glycol (2:1), and eluted from the column with isooctane:dichloromethane (7:3) before RIA.  $\Delta^4\text{A}$  was measured by a commercially available RIA kit (Diagnostics Systems Labs, Webster, TX). The within batch coefficient of variation of log<sub>e</sub> transformed hormone levels in blind replicate quality control samples were 15.0% for 11 $\beta$ OH and 3.9% for  $\Delta^4\text{A}$ .

Median hormone concentrations were calculated for cases and controls, and statistical significance of differences was tested by Wilcoxon rank-sum tests. Relationships of serum hormones to breast cancer risk were evaluated using conditional logistic regression. Women were stratified into tertiles based on their hormone levels relative to the distribution of hormone values in controls, and a set of categorical (dummy) variables was included in models. RRs were estimated as the antilogs of

Table 2 Median (5–95 percentile) serum hormone concentrations of cases and controls

	No. cases/ No. controls	Cases	Controls	P <sup>a</sup>
11 $\beta$ OH (nm)	53/106	4.6 (2.2–10.2)	4.1 (1.4–9.7)	0.31
Androstenedione (nm)	43/75	3.5 (1.4–6.4)	2.9 (1.1–5.6)	0.05
$\Delta^4\text{A}$ :11 $\beta$ OH <sup>b</sup>	39/66	0.7 (0.3–1.2)	0.7 (0.3–1.4)	0.95

<sup>a</sup> P from Wilcoxon rank-sum test (2-sided).

<sup>b</sup>  $\Delta^4\text{A}$ :11 $\beta$ OH excludes 5 cases and 12 controls who had bilateral oophorectomies.

the regression coefficients. Models also were fit using the continuous data to test for trends. To adjust for known breast cancer risk factors, time since menopause, height, weight, parity, and family history of breast cancer were included in models. Effect modification by age, time since menopause, and BMI (kg/m<sup>2</sup>) was evaluated by adding cross-product terms to models that included main effects as continuous variables. The association of the  $\Delta^4\text{A}$ :11 $\beta$ OH ratio with breast cancer risk was evaluated in women with intact ovaries at the time blood was collected. To conserve the number of participants who could be included in these analyses, unconditional logistic regression was used with adjustment for matching variables. All of the analyses were performed using SAS Statistical Software (16).

## Results

Characteristics of cases and controls are summarized in Table 1. Their mean age was 61.8 years (range, 50–76 years) and, except for two controls, all of the participants were white. Although cases were slightly taller than controls, their weights and BMIs did not differ. Cases' and controls' menstrual and reproductive histories also were similar. A positive family history of breast cancer among mothers, grandmothers, sisters, and aunts was reported by 28% of both cases and controls. Blood collection occurred, on average, 12.1  $\pm$  0.9 years after menopause in cases and 12.3  $\pm$  0.7 years in controls (P = 0.94). The time from blood collection to diagnosis in cases ranged from less than 1 to 9.5 years with a median of 2.8 years.

Cases had significantly higher serum  $\Delta^4\text{A}$  concentrations compared with controls (Table 2). Cases' 11 $\beta$ OH concentrations also were higher but nonsignificantly. After excluding 5 cases and 12 controls who reported prior bilateral oophorectomies, the  $\Delta^4\text{A}$ :11 $\beta$ OH ratio did not differ between groups. Adjusted for age, 11 $\beta$ OH and  $\Delta^4\text{A}$  concentrations were significantly (P < 0.001) and positively correlated in both cases (Spearman r = 0.50) and controls (Spearman r = 0.63).

After adjustment for known breast cancer risk factors, serum  $\Delta^4\text{A}$  concentration was significantly (trend P = 0.02) positively associated with breast cancer risk (Table 3). There also was a slight but nonsignificant (trend P = 0.20) gradient of increasing breast cancer risk with increasing serum concentration of 11 $\beta$ OH. RRs for women in the middle and highest tertiles were 1.2 (95% CI, 0.5–3.1) and 1.4 (95% CI, 0.5–3.6), respectively.

The relationship of serum  $\Delta^4\text{A}$  with breast cancer in women with at least one intact ovary (39 cases and 66 controls) was similar to that observed in the whole group. Adjusted RRs for women in the middle and highest versus the lowest tertile were 1.5 (95% CI, 0.5–4.7) and 2.4 (95% CI, 0.8–7.4), respec-

Table 3 Risk ratios (95% CIs) for breast cancer by tertile of serum hormone concentrations

Hormone		Tertile Categories <sup>a</sup>			P for trend <sup>b</sup>
		1 (referent)	2	3	
11 $\beta$ OHA	No. cases/No. controls	15/34	18/36	20/36	
	RR <sup>c</sup>	1.0	1.2 (0.5–2.8)	1.3 (0.5–3.1)	0.22
	Adjusted RR <sup>d</sup>	1.0	1.2 (0.5–3.1)	1.4 (0.5–3.6)	0.20
Androstenedione	No. cases/No. controls	7/24	12/23	24/28	
	RR <sup>c</sup>	1.0	2.0 (0.6–6.3)	2.4 (1.0–6.2)	0.05 <sup>e</sup>
	Adjusted RR <sup>d</sup>	1.0	1.6 (0.5–5.8)	2.4 (0.9–6.5)	0.02 <sup>e</sup>
$\Delta^4$ A:11 $\beta$ OHA <sup>f</sup>	No. cases/No. controls	11/21	13/22	15/23	
	RR <sup>g</sup>	1.0	1.1 (0.4–3.0)	1.3 (0.5–3.6)	0.95
	Adjusted RR <sup>h</sup>	1.0	1.2 (0.4–3.6)	1.2 (0.4–3.5)	0.99

<sup>a</sup> Tertile cutpoints were: 11 $\beta$ OHA (nM), 3.3, 5.0; androstenedione (nM), 2.4, 3.4;  $\Delta^4$ A:11 $\beta$ OHA, 0.6, 0.9.

<sup>b</sup> P (2-sided) for trend from model with log-transformed hormone concentration included as a continuous variable.

<sup>c</sup> RRs from conditional logistic regression matched on age, date, and time of day of blood collection.

<sup>d</sup> RRs from conditional logistic regression matched on age, date, and time of day of blood collection and adjusted for years since menopause, height, weight, parity, and family history of breast cancer.

<sup>e</sup> One influential outlier deleted.

<sup>f</sup>  $\Delta^4$ A: 11 $\beta$ OHA, excludes 5 cases and 12 controls who had bilateral oophorectomies.

<sup>g</sup> RRs from logistic regression adjusted for age, date, and time of day of blood collection.

<sup>h</sup> RRs from logistic regression adjusted for age, date, time of day of blood collection, years since menopause, height, weight, parity, and family history of breast cancer.

tively (trend  $P = 0.03$ ). Again, similar to the whole group, a slight but nonsignificant trend (trend  $P = 0.20$ ) of increasing risk with increasing concentration was apparent for 11 $\beta$ OHA. Adjusted RRs for increasing tertiles were 1.0, 1.0 (95% CI, 0.4–2.6), and 1.3 (95% CI, 0.5–3.1). There was little evidence, however, for an association of the  $\Delta^4$ A:11 $\beta$ OHA ratio with breast cancer risk in this subgroup. Compared with women in the lowest tertile, adjusted RRs for women in the middle and highest tertiles of the  $\Delta^4$ A:11 $\beta$ OHA ratio were 1.2 (95% CI, 0.4–3.6) and 1.2 (95% CI, 0.4–3.5), and the trend was not statistically significant ( $P = 0.99$ ).

Tests for interaction did not suggest that age, years since menopause, or BMI modified the associations of 11 $\beta$ OHA or the  $\Delta^4$ A:11 $\beta$ OHA ratio with breast cancer risk.

## Discussion

We reported previously (1, 2) that postmenopausal women in the Columbia, Missouri Serum Bank who had elevated serum concentrations of several androgens including DHEA, DHEAS,  $\Delta^4$ A, and testosterone were at an increased risk of breast cancer. In the current analysis, we evaluated associations of 11 $\beta$ OHA and the  $\Delta^4$ A:11 $\beta$ OHA ratio with risk to ascertain whether the adrenals or the ovaries were the predominant source of androgens in these women. Our finding that neither 11 $\beta$ OHA nor  $\Delta^4$ A:11 $\beta$ OHA was associated with risk suggests that both the ovaries and adrenals may contribute to elevated serum androgens in postmenopausal women who develop breast cancer.

Our findings are consistent with reports by others that hyperandrogenic women have mixed sources (adrenal and ovarian) of androgen production (17–19) as well as with findings from an autopsy series of increased frequencies of both adrenal cortical hyperplasia and ovarian stromal hyperplasia in women who die of breast cancer (20). Women in our study who developed breast cancer had elevated serum levels of  $\Delta^4$ A but not of 11 $\beta$ OHA, and decreased production of 11 $\beta$ OHA from  $\Delta^4$ A is a potential alternative explanation for our finding. Androgens have been reported to inhibit 11 $\beta$ -hydroxylation of steroids (21), and women in our study who developed breast cancer had elevated serum levels of several androgens including DHEA, DHEAS,  $\Delta^4$ A, and testosterone. However, adjustment for serum androgen concentrations did not materially change our findings for 11 $\beta$ OHA or the  $\Delta^4$ A:11 $\beta$ OHA ratio.

Therefore, if women who develop breast cancer have reduced 11 $\beta$ -hydroxylase activity, it does not appear to be secondary to their higher serum androgen concentrations. Decreased metabolic clearance of  $\Delta^4$ A is another potential explanation for our finding of elevated  $\Delta^4$ A but not 11 $\beta$ OHA. However, Kirschner *et al.* (22) directly assessed  $\Delta^4$ A metabolism in postmenopausal women with breast cancer and controls and found no differences in metabolic clearance rates or in the blood transfer constants of  $\Delta^4$ A to testosterone or to estrone.

We measured serum 11 $\beta$ OHA because it is more sensitive to adrenal stimulation and suppression tests compared with DHEAS and, consequently, is considered to be a better marker of adrenal androgen secretion (11–15). However, 11 $\beta$ OHA has been measured in ovarian follicular fluid (23, 24), and its concentration in the ovarian veins has been reported to be higher than in the ovarian arteries (25). The ovaries can concentrate steroids from the circulation (26), and intraovarian 11 $\beta$ OHA could be of adrenal origin. Alternatively, the ovaries might secrete small amounts of 11 $\beta$ OHA. In the report by Carmina *et al.* (15), the  $\Delta^4$ A:11 $\beta$ OHA ratio had 100% sensitivity and 84% specificity to identify adrenal hyperandrogenism in women with marked androgen excess. Our participants' serum androgen concentrations were within the normal range, and the  $\Delta^4$ A:11 $\beta$ OHA ratio may not discriminate sources of androgens as well at these levels.

Our study had several strengths. Serum was collected up to 10 years before diagnosis of breast cancer. We were able to match cases to controls on age and on date and time of blood collection and could account for several potential confounding variables including body weight, reproductive history, and family history of breast cancer in analysis. A limitation of our study was its relatively small sample size and consequent low power. However, serum concentrations of  $\Delta^4$ A exhibited strong positive associations with breast cancer in participants. Furthermore, our results are consistent with the limited data from an autopsy series that suggest both the ovaries and adrenals may contribute to elevated androgens in postmenopausal women who die of breast cancer (20).

This is the first epidemiological study to evaluate the relationships of serum 11 $\beta$ OHA and the  $\Delta^4$ A:11 $\beta$ OHA ratio with breast cancer. Larger and more definitive studies are needed to determine the source of excess androgens in post-

menopausal women who develop breast cancer. Findings from such studies could potentially provide clues to etiological factors for breast cancer.

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