

Plasma Adrenal Androgens and Risk of Breast Cancer in Premenopausal Women

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Abstract

Objectives: Plasma DHEA and its sulfate (DHEA-S) are positively associated with breast cancer risk in postmenopausal women; but the relationships have not been studied in detail in premenopausal women. We prospectively evaluated relationships between plasma levels of DHEA and DHEA-S in blood samples provided by a group of primarily premenopausal women and subsequent breast cancer, by use of case-control sampling from the Nurses' Health Study cohort. **Method:** Blood samples were collected from 1989 to 1990. Among women who were not postmenopausal at blood collection, 302 were diagnosed with breast cancer between blood collection and June 1998. Two controls were selected per case and matched with respect to age, menopausal status, month and time of day of blood collection, and fasting status at blood collection. Statistical analyses using conditional logistic regres-

sion were done to adjust for potential confounders. **Results:** At time of blood collection, the median age was 49 (10th to 90th percentiles 45 to 53). In multivariable analyses, the highest quartile of DHEA was associated with an odds ratio of breast cancer of 0.92 (95% confidence interval, 0.59-1.43) relative to the lowest quartile (*P* value for log-linear trend 0.11). A similar analysis revealed an odds ratio of 1.08 (0.69-1.69) for DHEA-S (*P* value for log-linear trend 0.83). No statistically significant interactions were noted according to certainty of menopausal status, age, or past oral contraceptive use. **Discussion:** Our analysis did not reveal a relationship between DHEA or DHEA-S and subsequent breast cancer in middle-aged premenopausal women. In the future, this relationship should be studied in younger women. (Cancer Epidemiol Biomarkers Prev 2004;13(6):1032-6)

Introduction

Substantial literature shows that endogenous hormones play a significant role in the etiology of breast carcinoma. Although much is known about the risks associated with endogenous estrogens, less is known about the effects of endogenous androgens. Plasma levels of the adrenal androgens DHEA and its sulfate (DHEA-S) are positively associated with breast cancer risk in postmenopausal women (1-3); but only one study (4) (15 cases) has assessed the role of these hormones prospectively in premenopausal women.

Androgens are thought to affect breast cancer risk either directly by increasing growth and proliferation of cancer cells (5), or indirectly via conversion to estrogen (6, 7). However, the adrenal androgens may have different effects depending on the estrogen environment. It has been suggested that DHEA and DHEA-S may exhibit anti-estrogen effects in high estrogen environments (8), but act like estrogens in low estrogen envi-

ronments (8, 9). It is, thus, plausible that DHEA and DHEA-S may lower the risk of breast cancer in premenopausal women.

We conducted a nested case-control study from the Nurses' Health Study cohort to evaluate prospectively the relationship between circulating plasma levels of DHEA and DHEA-S in premenopausal women and subsequent risk of breast cancer. We also examined the possibility that the association between androgen levels and breast cancer risk is modified by history of previous oral contraceptive use, age, and certainty of menopausal status at blood sampling.

Subjects and Methods

Study Population. The Nurses' Health Study cohort was established in 1976 when 121,700 female registered nurses, 30-55 years of age, completed and returned a mailed questionnaire. The cohort continues to be followed every 2 years by questionnaire to update exposure status and to identify cases of newly diagnosed disease. Data have been collected on many breast cancer risk factors, including height, weight, age at menarche and menopause, age at birth of first child, parity, postmenopausal hormone use, diagnosis of benign breast disease, and family history of breast cancer.

Received 12/1/03; revised 1/23/04; accepted 2/2/04.

Grant support: Public Health Service grant CA49449 from the National Cancer Institute, NIH, Department of Health and Human Services, and Public Health Service grant CA5T32CA009 from the National Cancer Institute (J. Page).

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From 1989 through 1990, blood samples were collected from 32,826 cohort members (27% of the original cohort) who were 43 to 69 years of age when blood was collected. Details about the blood collection methods have been published (10). Briefly, each woman arranged to have her blood drawn and then shipped, via overnight courier and with an ice pack to keep the sample cool, to our laboratory, where it was processed and separated into plasma, red blood cell, and white blood cell components. Within 26 hours of being drawn, 97% of the samples were received in our laboratory. The stability of estrogens and androgens in whole blood for 24 to 48 hours has been documented previously (11). Since collection, samples have been archived at -130°C or colder in continuously monitored liquid nitrogen freezers. As of 1998, the proportion of women still participating and available for follow-up among the 32,826 who had provided a blood sample was 99.8%.

The study was approved by the Committee on the Use of Human Subjects in Research at the Brigham and Women's Hospital. Both case and control subjects in this analysis are women who, at blood collection, were not documented to be postmenopausal. The participants were defined as postmenopausal if they reported having a natural menopause or a bilateral oophorectomy. Women who reported a hysterectomy with either one or both ovaries remaining were defined as postmenopausal when they were 56 years old (if a nonsmoker) or 54 years old (if a current smoker), ages at which natural menopause had occurred in 90% of the respective cohorts; and as premenopausal when they were less than or equal to 48 years old (if a nonsmoker) or less than or equal to 46 years old (if a current smoker), ages at which natural menopause had occurred in 10% of the cohorts. Women were classified of uncertain menopausal status if their ages fell between these cut-points. Case women were those who had reported no cancer diagnosis before blood collection and who were diagnosed with breast cancer after blood collection but before June 1, 1998. Overall, 302 cases of breast cancer (216 invasive, 72 *in situ*, and 14 unknown) were reported from among the 10,353 women eligible at baseline. (The other 22,473 women were not eligible because they were postmenopausal.) All cases of breast cancer were confirmed by medical record review with two exceptions. (Because of the high confirmation proportion, all cases were retained in the analysis.) The median (10th to 90th percentiles) time from blood collection to diagnosis was 55 months (15 to 93). Two control subjects were matched per case subject by age (± 2 years), month of blood collection, time of day that blood was drawn (± 2 hours), and fasting status at the time of blood collection (≥ 10 hours since a meal versus < 10 hours or unknown). Ninety-three percent of control matches were exact; the most relaxed match was within ± 5 years of age, ± 3 months of blood collection from case subjects, and ± 7 hours for time of blood collection. After all exclusions, there were 302 cases and 591 controls.

Laboratory Analyses. DHEA was measured by ELISA (Diagnostic Systems Laboratories, Webster, TX). The assay employs the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific

for DHEA has been pre-coated onto a microtitre plate. After the addition of samples, standards, controls, and conjugates to the wells, DHEA is sandwiched between the immobilized antibody and the enzyme-linked antibody specific to DHEA. After washing to remove unbound substances, substrate is added and a color is generated that is proportional to the amount of DHEA present in the sample. On the basis of masked quality control samples (10% of the total number of samples) inserted among the case and control blood samples, the intra-assay coefficient of variation for DHEA was 6.5%. The inter-assay coefficient of variation was 8.8%.

DHEA-S is measured by a coated-tube RIA (Diagnostic Systems Laboratories). The principle is based on competition between a radioactive and nonradioactive antigen for a fixed number of antibody binding sites. The amount of ^{125}I -labeled DHEA-S bound to the antibody is inversely proportional to the concentrations of the DHEA-S present in the sample. The separation of free and bound antigen is achieved by decanting or aspirating the antibody-coated tubes. On the basis of masked quality control samples (10% of the total number of samples) inserted among the case and control blood samples, the intra-assay coefficient of variation for DHEA-S was 2.1%. The inter-assay coefficient of variation was 3.1%.

Reproducibility Study. The reproducibility of DHEA and DHEA-S in premenopausal women was studied over a 3-year period in a sample of 113 women from the Nurses' Health Study II with mean age 41.7 (range 34 to 49) at the onset. The intraclass correlation coefficient for DHEA for three follicular phase samples, three luteal phase sample, and for all six samples were 0.54, 0.66, and 0.59, respectively. A similar analysis for DHEA-S revealed intraclass correlation coefficients of 0.92, 0.79, and 0.82, respectively. In a reproducibility study of postmenopausal women in the NHS, the intraclass correlation coefficient for DHEA and DHEA-S were 0.75 and 0.88, respectively (12).

Previous analyses of DHEA/DHEA-S in the Nurses' Health Study were done with different assays in a different laboratory. A subset analysis of 15 specimens was done to compare the assays. The mean ratios (95% limits of agreement) of the current assay to the previous were 1.90 (1.40, 2.57) and 0.48 (0.33, 0.69) for DHEA and DHEA-S, respectively. However, the Pearson's correlation coefficients were 0.95 and 0.93, respectively.

Data Analysis. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) (13).

We additionally controlled for potential confounders that were not part of the matching scheme. Age at first birth and parity were controlled by creating categories for nulliparous women, parity between 1 and 4 and age at first birth less than 25, parity between 1 and 4 and age at first birth 25 to 29, parity between 1 and 4 and age at first birth greater than 29, parity greater than 4 and age at first birth less than 25, parity greater than 4 and age at first birth 25 to 29, and parity greater than 4 and age at first birth greater than 29. A categorical variable for age at menarche was used with categories for less than age 12, age 12, age 13, and age greater than 13. Indicator variables were also created for certainty of menopausal

status (definitely premenopausal versus uncertain menopausal status), and history of a first degree family member with breast cancer. To more appropriately control for confounding by continuous covariates (mean yearly energy-adjusted alcohol intake between 1980 and 1994 and before index date, mean yearly energy-adjusted dietary folate intake between 1980 and 1990 and before index date, and body mass index at age 18), regression splines (natural cubic splines) (14, 15) with four degrees of freedom were used to smooth the relationships with the log-odds of breast cancer. We additionally controlled for age at the time of blood collection (entered as a linear term) because the matching on this variable was not perfect. A few covariate values (body mass index at age 18, age at first birth, and dietary folate) were missing for some study participants (less than 9%). Other covariates had less than 1.3% missing values. To retain their remaining data for analysis, we input missing values with the median for some variables, and created a missing value category for age at first birth.

We conducted tests for trend by modeling the hormone level as a continuous covariate and calculating a Wald statistic (13). All *P* values are based on two-sided tests. The software used for statistical analysis were SAS release 8.2 (16) and S-plus version 6 (17).

Results

At the time of blood sampling, the women in this study had a median age of 49 (10th and 90th percentiles 45 to 53). Table 1 shows the distribution of risk factors for breast cancer at the time of blood sampling among case women and matched controls. These covariates were reasonably similar in distribution between the two groups of women except for folate consumption, which was lower in women who later developed breast cancer relative to the control women, and family history (first degree relatives) of breast cancer, which was

Table 1. Distribution of covariates in case and matched control study participants

Covariate and unit of measure	Cases	Controls
	Median (10th to 90th percentiles)	Median (10th to 90th percentiles)
DHEA, (ng/dL)	310 (139-634)	312 (136-648)
DHEA-S (µg/dL)	151 (70-291)	149 (63-292)
Age at blood draw (years)	49.3 (45.2-53.8)	49.3 (45.0-53.8)
BMI at age 18 (kg/m ²)	20.6 (18.2-24.3)	20.9 (18.5-25.6)
Age at menarche (years)	12 (11-14)	12 (11-14)
Age at first birth (years)	24 (21-29)	24 (21-28)
Mean yearly alcohol consumption (g/d)	2.0 (0-14.9)	2.5 (0-15.3)
Dietary folate (g/d)	339 (219-607)	365 (217-613)
Family history of breast cancer (in first degree relatives)*	47 (15.1)	65 (11.0)
Use of female hormones in the 3 months before blood collection*	63 (21)	120 (20.3)

NOTE: There were 302 cases and 591 controls. To convert DHEA to nmol/L, multiply by 0.0347, and to convert DHEA to µmol/L, multiply by 0.0271.

*Number (percentage) shown.

higher among women who subsequently developed breast cancer. Pearson's correlation coefficient between DHEA and DHEA-S among control patients was 0.60 ($P < 0.001$).

Table 2 summarizes the conditional logistic regression analysis of the relationship between DHEA(S) and subsequent breast cancer. Women in the top quartile of plasma DHEA had a slightly reduced odds of breast cancer relative to those in the lowest quartile that was not statistically significant [OR (95% CI 0.92 (0.59-1.43)]. Women in the top quartile of plasma DHEA-S had a slightly elevated risk of breast cancer relative to women in the lowest quartile that was not statistically significant [OR (95% CI 1.08, 0.69-1.69)].

The relationships between DHEA and DHEA-S and breast cancer were not appreciably modified by certainty of menopausal status (definitely premenopausal versus uncertain), age greater than or less than 50, whether women had used oral contraception during their lifetime, nor by whether women were current users of female hormones (tests for interaction, $P > 0.05$).

The results did not change much when analyses were restricted to those matched sets with invasive breast cancer cases only, estrogen receptor cases only, cases diagnosed at least 2 years after blood draw, and cases that were premenopausal at diagnosis. However, among case-control sets with a postmenopausal case at breast cancer diagnosis, DHEA was negatively associated with breast cancer incidence (P value for linear trend, 0.04), although none of the individual relative risks were statistically significant (see Table 3).

Discussion

The prospective epidemiologic study presented here does not show evidence of a relationship between circulating plasma levels of DHEA and DHEA-S in older premenopausal women and subsequent risk of breast cancer. These results were largely unchanged when we restricted the analysis to invasive cancers or to estrogen receptor positive cancers. To explore the possibility of occult breast cancer having an impact on the results, we studied the relationships after restricting the analysis to matched sets with breast cancer that occurred 2 or more years after blood sampling; the results were not sensitive to this restriction (see Table 3). Although our study population consisted of older premenopausal women, including a significant proportion for whom the certainty of menopausal status was not established, restricting the analysis to women who were definitely premenopausal did not influence our conclusions. Also, the results were not modified by whether or not women had had a history of prior oral contraceptive use.

This is the first large prospective evaluation of the relationship between adrenal androgens and subsequent breast cancer in women who are predominantly premenopausal. Helzlsouer et al. (4) conducted a small prospective study that assessed the role of DHEA in premenopausal women in relation to subsequent breast cancer. It included 15 cases of premenopausal breast cancer and 29 matched controls; and found that DHEA in the highest tertile was associated with a 60% lower risk relative to the lowest tertile. In addition to being

Table 2. OR of breast cancer and 95% CI by quartile of adrenal hormone levels among predominantly premenopausal women in the Nurses' Health Study

Hormone level	Quartile categories				P value for trend
	1	2	3	4	
DHEA, (ng/dL)	<200	200-307	308-450	≥451	
No. of cases/No. of controls*	76/138	72/143	74/140	73/144	
Simple OR [†] (95% CI)	1.0 (referent)	0.94 (0.65-1.49)	0.99 (0.65-1.49)	0.93 (0.61-1.42)	0.17
Adjusted OR [‡] (95% CI)	1.0 (referent)	0.94 (0.62-1.43)	0.96 (0.62-1.48)	0.92 (0.59-1.43)	0.11
DHEA-S, (μg/dL)	<96	96-146	147-218	≥219	
No. of cases/No. of controls	64/141	80/146	83/143	69/141	
Simple OR [†] (95% CI)	1.0 (referent)	1.18 (0.79-1.75)	1.28 (0.86-1.91)	1.08 (0.71-1.65)	0.78
Adjusted OR [‡] (95% CI)	1.0 (referent)	1.25 (0.83-1.90)	1.29 (0.85-1.96)	1.08 (0.69-1.69)	0.83

NOTE: To convert DHEA to nmol/L, multiply by 0.0347, and to convert DHEA to μmol/L, multiply by 0.0271.

*Numbers do not add up to 302 cases and 591 controls due to missing DHEA(S) data.

[†]Conditional logistic regression model controlling for matching factors only.

[‡]Conditional logistic regression additionally controlling for age at first birth/parity, age at menarche, certainty of menopausal status (definite premenopausal versus uncertain), first degree family history of breast cancer, age at blood draw (modeled as a linear continuous variable), mean alcohol intake, mean folate intake, and body mass index at age 18 (the latter three variables modeled as continuous variables with natural cubic splines).

quite small, their sample consisted of much younger women (ages 24 to 43) at the time of blood collection. However, our results are consistent with the findings of two small prospective studies that assessed the role of premenopausal testosterone and subsequent breast cancer (18, 19).

Others have investigated these relationships in postmenopausal women (1-3, 20). In a reanalysis of nine prospective studies that included cases and controls from the Nurses' Health Study, both DHEA and DHEA-S were associated with statistically significantly elevated risks of breast cancer in postmenopausal women who were ages 58 to 72 (20). Our finding that DHEA was negatively associated with breast cancer incidence among case-control sets with a case that was postmenopausal at diagnosis conflicts with this body of literature and, thus, is most likely to be a chance finding. It has

been suggested that DHEA and DHEA-S may exhibit anti-estrogen effects in high estrogen environments (8), but act like estrogens in low estrogen environments (8, 9), such as in postmenopausal women. Relative to DHEA and DHEA-S, which are the primary circulating adrenal androgens, these dual effects are likely to be stronger for their metabolite 5-androstenediol (8, 21, 22).

One possible reason that we did not find a clear relationship between DHEA/DHEA-S and breast cancer is that this group is somewhat transitional in age between younger premenopausal (in whom the relationship may be negative) and postmenopausal women (in whom the relationship is positive). DHEA-S levels decline linearly with age (23-27), resulting in serum levels in women in their 70s that are approximately 20-25% of those in 20- to 30-year-old women (24, 25, 27). However, unlike the abrupt reduction in estrogen levels seen with

Table 3. OR* of breast cancer subgroups and 95% CI by quartile of adrenal hormone levels among predominantly premenopausal women in the Nurses' Health Study

Hormone level	No. of cases/ No. of controls	Quartile categories				P value for trend
		1	2	3	4	
DHEA, (ng/dL)		<200	200-307	308-450	≥451	
Invasive cancers only	209/398	1.0 (referent)	1.01 (0.60-1.69)	1.13 (0.66-1.94)	0.94 (0.54-1.62)	0.06
ER positive cases only [†]	157/304	1.0 (referent)	0.80 (0.43-1.46)	1.21 (0.66-2.23)	0.82 (0.40-1.50)	0.07
Cases ≥2 years after blood	242/465	1.0 (referent)	0.81 (0.51-1.29)	0.90 (0.56-1.45)	0.95 (0.58-1.57)	0.15
Premenopausal cases only ^{‡,§}	101/195	1.0 (referent)	1.11 (0.52-2.37)	1.26 (0.59-2.68)	1.12 (0.53-2.40)	0.61
Postmenopausal cases only ^{‡,§}	129/252	1.0 (referent)	0.82 (0.47-1.43)	0.75 (0.41-1.39)	0.74 (0.39-1.43)	0.04
DHEA-S, (μg/dL)		<96	96-146	147-218	≥219	
Invasive cancers only	211/404	1.0 (referent)	1.32 (0.80-2.20)	1.39 (0.83-2.34)	1.10 (0.63-1.91)	0.79
ER positive cases only ^{†,}	159/309	1.0 (referent)	1.22 (0.68-2.19)	1.41 (0.78-2.54)	1.08 (0.58-2.02)	0.73
Cases ≥2 years after blood	244/470	1.0 (referent)	1.11 (0.69-1.76)	1.37 (0.87-2.16)	1.09 (0.66-1.78)	0.67
Premenopausal cases only ^{‡,§}	101/197	1.0 (referent)	1.53 (0.69-3.41)	1.49 (0.67-3.30)	1.49 (0.67-3.29)	0.62
Postmenopausal cases only ^{‡,§}	131/254	1.0 (referent)	0.89 (0.51-1.53)	1.01 (0.57-1.80)	0.86 (0.45-1.67)	0.94

NOTE: To convert DHEA to nmol/l, multiply by 0.0347, and to convert DHEA to μmol/l, multiply by 0.0271.

*Conditional logistic regression additionally controlling for age at first birth/parity, age at menarche, certainty of menopausal status (definite premenopausal versus dubious), first degree family history of breast cancer, age at blood draw (modeled as a linear continuous variable), mean alcohol intake, mean folate intake, and body mass index at age 18 (the latter three variables modeled as continuous variables with natural cubic splines).

[†]ER positive is estrogen receptor positive.

[‡]Simple (unadjusted for other covariates) ORs from conditional logistic regression used due to sparse data.

[§]Case patients with breast cancer were either premenopausal or postmenopausal at diagnosis.

^{||}Continuous covariate fitted as linear terms because of convergence problems with fitting the natural cubic splines.

menopause, the slope of declining serum DHEAS levels versus age remains constant over time (28). The median age in this population was 49 (range 42 to 59). The medians (12.5%, 87.5% percentiles) for DHEA and DHEA-S in this sample were 312 ng/dL (148, 601) and 149 µg/dL (67, 274), respectively. In postmenopausal women in the Nurses' Health study cohort (1) who were on average 12 years older, median DHEA and DHEA-S were much lower, but the assays used in that study were different from those used in this one, precluding direct comparison of values. Although not suggested by this analysis, an etiologic role of DHEA-S might be seen primarily at lower levels. Major strengths of this study are its prospective nature as well as its large size, the largest of its kind done to date.

In summary, our study did not demonstrate a relationship between plasma levels of DHEA and DHEA-S and subsequent risk of breast cancer in middle-aged premenopausal women. Future studies should evaluate these relationships (including other androgens as well as that of 5-androstenediol) in younger women.

Acknowledgments

We are indebted to the participants in the Nurses' Health Study for their continuing dedication and commitment.

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Cancer Epidemiol Biomarkers Prev 2004;13:1032-1036.

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