Dehydroepiandrosterone Sulfate and Breast Cancer Risk

Elizabeth Barrett-Connor, Nancy Lee J. Friedlander, and Kay-Tee Khaw

ABSTRACT

It has been suggested that dehydroepiandrosterone (DHEA) and its sulfate ester, dehydroepiandrosterone sulfate (DHEAS), have a protective effect against breast cancer. In our investigation, DHEAS levels were measured in plasma obtained and frozen in 1972–1974 from 534 women aged 50–79 yr. This group, which has been followed for 15 yr, included 21 incident cases of breast cancer, 20 cases with earlier diagnosis, and ten cases with unknown date of onset who were identified from death certificates only. Two sets of analyses were done: one using all women and one which excluded women using estrogen. No significant differences in age-adjusted rates of breast cancer by DHEAS fertile women and noncases. Age-adjusted rates of breast cancer by DHEAS tertile also showed no significant trends or differences among tertiles for any case type. A multivariate model in which the DHEAS level was adjusted for age, body mass index, estrogen use, and cigarette smoking status also showed no significant association between DHEAS and risk of breast cancer. These results do not support a protective role for plasma DHEAS in breast cancer risk in postmenopausal women.

INTRODUCTION

The biological significance of DHEA and its sulfate ester DHEAS remains unknown, although 25 yr have passed since Baulieu et al. (1) reported that DHEAS is secreted in large quantity by the human adrenal gland.

Several lines of evidence suggest that low levels of this weak androgen might promote and high levels might prevent breast cancer. Schwartz and coworkers (2–4) reported that long-term DHEA treatment inhibited the development of spontaneous breast cancer in obese and nonobese C3HA/A mice. In humans, DHEAS levels lower in overweight and older adults, two attributes associated with an increased risk of breast cancer. Several case comparison studies have shown lower plasma levels of DHEA or DHEAS in patients with advanced breast cancer (5, 6). Several case comparison studies have shown lower plasma levels of DHEA or DHEAS in patients with advanced breast cancer (7–11). In one study of 11 women with operable breast cancer, 24-h plasma levels of DHEA and DHEAS were lower in premenopausal patients and higher in postmenopausal patients than in normal women (11). As in all cross-sectional studies it is uncertain whether observed differences preceded or followed the disease.

The results of a prospective study by Bulbrook et al. (12) are compatible with the hypothesis that women with subnormal DHEAS levels are at increased risk of breast cancer. In that study 24-h urine collections were obtained from approximately 5000 women who were then followed for breast cancer. Urinary excretion of androsterone and etiocholanolone, two major metabolites of DHEA, was lower in the 27 women who developed breast cancer over the next 9 yr than in 187 women matched for other risk factors who did not. In a later report, when the total number of breast cancers was 48, Farewell et al. (13) reported that the mean of log of the 24-h urinary DHEA was lower (2.30 ± 0.101) in precancerous women than in 4663 women who did not develop cancer (2.47 ± 0.017), but these differences were not statistically significant; untransformed data were not shown.

The postulated anticancer effects of DHEA/DHEAS are biologically plausible: DHEA could repress cellular DNA synthesis by reducing ribonucleotide and deoxyribonucleotide synthesis as a result of glucose-6-phosphate dehydrogenase inhibition; could exert protection by virtue of the antiobesity effects; or could be protective via conversion into estrone (2).

In this paper we report the absent association of plasma DHEAS and breast cancer, using both cross-sectional and prospective methods, in a population-based cohort of older women.

MATERIALS AND METHODS

Between 1972 and 1974, 82% (n = 6110) of all adult residents of Rancho Bernardo, CA, a white upper-middle-class community in southern California, participated in a heart disease risk factor survey as part of a Lipid Research Clinic Prevalence Study. All participants had a standardized interview, which included questions about personal history of cigarette smoking and exogenous gonadal hormone use. Height and weight were measured with the subjects wearing light clothing and no shoes.

Plasma used to determine hormone levels was obtained at the baseline visit in 1972–1974 between 7:00 and 11:00 a.m.; 95% of participants had fasted as requested 12 to 16 h prior to venipuncture. Plasma was then frozen at −70°C, until thawed for sex hormone assays 12 to 15 yr later. Previous work in this laboratory had demonstrated that DHEAS levels show no deterioration over a period of 15 yr when sera are frozen and stored in tightly sealed containers (14). The choice and number of samples assayed were limited by availability of plasma and cost constraints. Hormone assays were performed without knowledge of the subject's age or current or subsequent disease status in a research laboratory using a radioimmunoassay method (15). The sensitivity and the intraassay and interassay coefficients of variation for DHEAS were 0.02 μg/ml, 5.0%, and 10.0%, respectively.

This cohort has been followed annually for vital status with 99.9% ascertainment. Death certificates have been obtained for all decedents and coded by a certified nosologist according to the International Classification of Diseases, Ninth Revision (16). The incidence of nonfatal breast cancer was first ascertained in 1982, when 93% of all surviving participants returned a mailed questionnaire which asked about site-specific cancer and the year of first diagnosis. Self-reported cancer in all sites except nonmelanoma skin cancer was followed by a letter requesting permission to obtain hospital records for validation. The diagnosis of nonfatal cancer and the year of diagnosis were accepted if confirmed by the hospital record and/or a pathology report. The diagnosis was confirmed in all 14 reported nonfatal breast cancers with onset between 1975 and 1982 and in 100% of cases with earlier incidence for whom records were available. A similar morbidity questionnaire was mailed in 1984 with a 96.7% response rate from survivors. From 1984 to June 1987, a standardized interview was obtained from approximately 80% of surviving members of the original cohort, which also asked about site-specific cancer and the year of first diagnosis. No validation was attempted, based on the high validation rate with the first questionnaire.
Analyses were done for the entire population of women described above (n = 534) and for the subgroup who were not taking exogenous estrogen (n = 442). Age, obesity, cigarette smoking, and exogenous estrogens were considered as covariates, because each has been said to be associated with altered DHEAS levels and risk of breast cancer. Obesity was estimated using the body mass index, or BMI [weight (kg)/ height (m)]. For continuous variables, crude and age-adjusted means were compared using t tests and analyses of variance and covariance. For categorical variables, differences in rates were compared using the \( \chi^2 \) statistic. Relative risks were calculated after adjustment for age, BMI, cigarette smoking, and estrogen use, using Cox proportional hazards regression (17). Statistical analyses were performed using the Statistical Package for the Social Sciences (18) and BMDP (19).

RESULTS

There were 534 women aged 50 to 79 yr at baseline for whom DHEAS levels from blood obtained in 1972–1974 were available. Among these women, 51 breast cancer cases were identified. This total group of cases was divided into three subgroups: (a) incident cases (n = 21), participants whose breast cancer was first diagnosed at least 1 yr after baseline examination; (b) prevalent cases (n = 20), participants who were diagnosed as having breast cancer before baseline or within 1 yr after baseline; (c) cases with unknown date of onset (n = 10), cases identified from death certificates only, whose date of diagnosis was unknown. The 483 comparison women for whom hormone data were available were free of breast cancer as of June 1987.

Table 1 shows baseline mean DHEAS levels and age, BMI, current cigarette smoking status, and estrogen use by breast cancer status. There were no significant differences in DHEAS levels in incident, prevalent, or total cases versus noncases. Cases and noncases also did not differ significantly in mean age or by cigarette smoking status. The only difference in cases versus noncases was seen in women with breast cancer of unknown date of diagnosis, who were thinner than noncases (crude, \( P < 0.01 \); age adjusted, \( P = 0.07 \)). Estrogen use was not significantly associated with breast cancer. Women with incident breast cancer had nonsignificantly higher rates of baseline estrogen use, while women with prevalent cancer were least likely to be taking estrogen.

Because women taking estrogen were leaner, had lower levels of DHEAS, and may be at increased risk of breast cancer, they were excluded and analyses were repeated. As shown in Table 1, the results were essentially unchanged; i.e., there were no significant differences in mean DHEAS levels, age, or smoking status among incident, prevalent, or total cases and noncases. BMI was again somewhat lower in cases with unknown date of diagnosis than in noncases (\( P = 0.08 \)), and prevalent cases had a slightly higher BMI than did noncases (\( P = 0.09 \)).

Table 2 shows age-adjusted breast cancer rates by tertile of DHEAS, again for all women, and after excluding women taking estrogen. There were again no significant differences, nor were there any consistent trends.

When the independent effect of each of these variables on risk of breast cancer was assessed by the Cox proportional hazards model (Table 3), DHEAS, age, estrogen use, and smoking status did not significantly affect risk. The standard deviation increase of DHEAS, 0.6 \( \mu \text{g}/\text{ml} \), was associated with a 0.93 relative risk for incident breast cancer (\( P = 0.79 \), 95% confidence interval = 0.55–1.58) and 0.90 for all breast cancer (\( P = 0.54 \), 95% confidence interval = 0.64–1.27). The statistically significant association noted above was confirmed in this multivariate model. A higher BMI was associated with lower risk (relative risk = 0.40; \( P = 0.03 \)) in the fatal cases with unknown date of onset, compatible with cancer-related weight loss.

DISCUSSION

These data do not support any effect of plasma DHEAS on breast cancer risk in postmenopausal women. In this cohort, DHEAS levels were not significantly associated either cross-sectionally with prevalent breast cancer or prospectively with incident breast cancer. There were also no consistent relations observed within subsets of cases nor consistent dose-response associations by tertiles of hormone levels.

Although the power of this study, with 51 total cases, was modest, the absence of any dose-response trend in the tertile analyses also points against a true association. Because DHEAS was measured only once at baseline, misclassification due to intraindividual variability could have masked a weak association. Although the power of this study, with 51 total cases, was modest, the absence of any dose-response trend in the tertile analyses also points against a true association. Because DHEAS was measured only once at baseline, misclassification due to intraindividual variability could have masked a weak association. DHEAS varies little from day to day or by hour of day (24). Although the power of this study, with 51 total cases, was modest, the absence of any dose-response trend in the tertile analyses also points against a true association. Because DHEAS was measured only once at baseline, misclassification due to intraindividual variability could have masked a weak association. DHEAS varies little from day to day or by hour of day (24). Although the power of this study, with 51 total cases, was modest, the absence of any dose-response trend in the tertile analyses also points against a true association. Because DHEAS was measured only once at baseline, misclassification due to intraindividual variability could have masked a weak association.
breast fluid than in plasma (21), there is a strong correlation between DHEAS in blood and breast tissue in females with or without breast cancer (22).

Most other studies that reported significant differences in plasma DHEAS levels in breast cancer cases have been cross-sectional studies of predominantly premenopausal women (7–11), while the present cohort was postmenopausal at baseline. It is possible that DHEAS levels earlier in life influence breast cancer risk after the menopause. It is also possible that there may be more complex interactions with other sex hormones or in the intracellular metabolism of DHEA and DHEAS. Thus, while this prospective study provides no evidence for a protective role for circulating DHEAS in breast cancer risk in postmenopausal women, these results cannot exclude small biologically important associations.

REFERENCES


9. Wang, D. Y., Bulbrook, R. D., Herian, M., and Hayward, J. L. Studies on the sulphate esters of dehydroepiandrosterone and androstenedione in the intracellular metabolism of DHEA and DHEAS. Thus, while this prospective study provides no evidence for a protective role for circulating DHEAS in breast cancer risk in postmenopausal women, these results cannot exclude small biologically important associations.
DHEAS AND BREAST CANCER RISK


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