Relationship of Prediagnostic Serum Levels of Dehydroepiandrosterone and Dehydroepiandrosterone Sulfate to the Risk of Developing Premenopausal Breast Cancer

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ABSTRACT

Dehydroepiandrosterone and dehydroepiandrosterone sulfate are steroids which may be associated with the development of breast cancer. To examine the association between serum levels of dehydroepiandrosterone and dehydroepiandrosterone sulfate and the risk of developing premenopausal breast cancer, we measured hormone levels in 15 women who donated blood to a community-based serum bank in 1974 and who subsequently developed premenopausal breast cancer and in 29 matched controls from the same group of volunteers. The mean serum level of dehydroepiandrosterone among cases was 10% lower than among controls. The risk of developing breast cancer for women in the highest tertile compared with the lowest tertile of serum dehydroepiandrosterone was 0.40 with a suggestion of a dose-response trend with increasing levels. No consistent association between dehydroepiandrosterone sulfate and the risk of premenopausal breast cancer was evident. In contrast to postmenopausal breast cancer, a protective effect of dehydroepiandrosterone against premenopausal breast cancer is suggested, but because of the small sample size, the results of this study need to be replicated by others.

INTRODUCTION

DHEA3 and DHEAS are major secretory products of the adrenal gland. DHEA is metabolized to steroids such as testosterone and estrogen and is an uncompetitive inhibitor of glucose-6 phosphate dehydrogenase. A cancer-preventive effect of DHEA has been demonstrated in animal studies and suggested by some epidemiological studies (1, 2). Oral supplementation with DHEA has been reported to inhibit the formation of tumors, including virus-induced mammary cancers in mice (3–6).

The blood levels of DHEA and DHEAS decline with age as the incidence of most cancers increases (3). In addition, an inverse association with bladder and other cancers has been reported (3, 7). However, we recently reported that the risk of postmenopausal breast cancer was significantly higher in women with elevated prediagnostic serum levels of DHEA compared with controls (8). The present study was designed to assess the association between prediagnostic serum levels of DHEA and DHEAS and the risk of developing premenopausal breast cancer.

MATERIALS AND METHODS

A nested case-control study was conducted using serum samples from residents of Washington County, MD, who participated in the establishment of a serum bank in 1974. Blood samples were collected from 20,305 persons identified in a private census of Washington County in 1975, representing 30% of that population. Nonsmokers, women, and the better educated were more likely to have donated samples. The age range of the participants was 11 to 98 with the highest participation rate among those aged 55–64 yr. Of these samples, 11,009 were collected from women over the age of 18. A brief questionnaire was administered to all participants at the time of blood collection. The questionnaire assessed basic demographic information, smoking history, and information on all medications, including exogenous hormones, taken during the 48 h prior to blood sampling. Premenopausal women were also asked the number of days from the beginning of their last menstrual cycle. Parity status at the time of blood donation was obtained from information collected at private censuses conducted in 1963 and 1975 and from a search of vital records for the county. Information on parity status is available for all cases and 20 of 29 controls.

Incident premenopausal breast cancer cases were identified by linkage of the Washington County Cancer Registry with the list of donors to the serum bank. Because Washington County Hospital is the only general hospital in the county and because it has a well-equipped oncology service, surveillance of its records and of death certificates is estimated to identify about 90% of the cancer cases among county residents. Only cases identified on the medical record as having menstruated within 30 days of the time of diagnosis were included in the study. During the years of 1975 to 1986 inclusive, 26 new cases were identified in premenopausal women. The diagnoses were confirmed by reviews of the pathology reports.

For each case, two controls were selected who were alive and free from known cancer (with the exception of nonmelanoma skin cancer) at the time of diagnosis of the cases. Cases and controls were matched on sex, race (all were white), age within 1 yr, number of days from the beginning of the last menstrual period (within 1 day), time of day blood was collected, and within 2 h for the interval between blood collection and the previous meal.

Seven cases, but none of the controls, reported taking oral contraceptives at the time of blood donation. These seven cases and their controls were excluded from analysis because of reported effects of oral contraceptives on serum hormone levels (9, 10). An additional case and her controls were excluded because of a prolonged time since her last menstrual period at the time of blood donation (greater than 180 days). Of the remaining 18 case-control sets, 15 had sufficient serum for DHEA and DHEAS assays for the case and at least one matched control.

Laboratory Assays. Serum was prepared from blood samples within 24 h of collection and usually within 6 h. The sera were maintained at −70°C until they were thawed for the preparation of aliquots for another study. The remaining sera were maintained on ice for less than 3 h before refreezing at −70°C. Samples were maintained at −70°C until assays for DHEA and DHEAS were performed. Coded sets, each consisting of a case and matched controls, were assayed on the same day. Quality control samples were included in some sets. All assays were done in triplicate, and the laboratory personnel were unaware of the coding within sets. If a sample required replication, the entire set was reassayed.

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3 The abbreviations used are: DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate.
DHEA and DHEAS assays were performed using radioimmunoassay kits from Wien Laboratories, Succasunna, NJ. These reagents were selected by comparison with combined chromatographical and enzymatic assays for DHEA and DHEAS (11). The kits were used as suggested by the manufacturer except that DHEA was extracted from serum utilizing a 1:1 (v:v) mixture of dichloromethane and hexane. Distilled water extraction blanks were included in each DHEA assay. Known quality control samples were included in each assay. Standards were performed in quadruplicate, and maximum binding was determined in 6 samples per assay. A log regression was used to calculate the concentration of steroid in the samples. The coefficient of variation from reference serum was 2.3% for DHEA and 2.7% for DHEAS.

Statistical Analysis. The SAS package was used to perform all analyses (12, 13). DHEA and DHEAS levels were treated as both continuous and categorical variables. The analysis of variance procedure was used to perform a paired t test with 2:1 matching to assess the mean difference in serum hormone levels between cases and controls. Because the distributions for DHEA and DHEAS were skewed, natural log transformations were used for statistical tests when DHEA and DHEAS were treated as continuous exposure variables. Conditional logistic regression analysis was used to assess and adjust for potential confounders of the association between DHEA and DHEAS levels and the risk of breast cancer such as smoking.

Tertile cutpoints for DHEA and DHEAS were based on the distributions in the controls. Odds ratios were calculated from the regression coefficients of the conditional logistic regression analysis, with the lowest tertile of hormone levels as the reference value. Trends were evaluated by regression analysis using the method described by Breslow and Day (14). Exposure scores were assigned according to the median value for each tertile. Reported P values represent two-tailed tests.

RESULTS

The distributions of selected characteristics among cases and controls are presented in Table 1. The age range of the cases at the time of blood donation is 24 to 43 yr. The age range at the time of diagnosis is 28 to 49 with a mean age of 44 yr. As a result of matching, cases and controls have the same mean age, similar mean days from the beginning of the menstrual cycle, and similar hours between the time of blood collection and the previous meal. Mean blood pressure is slightly higher, and a history of cigarette smoking is more common among cases. Cases were more likely to be parous than controls. None of the observed differences are statistically significant.

The mean levels and the range of values of DHEA and DHEAS among cases and controls are presented in Table 2. The mean serum level of DHEA among women who subsequently developed premenopausal breast cancer is 10.4% lower than that among controls. There is no difference in DHEAS levels between cases and controls.

The odds ratios for the development of breast cancer for the middle and highest tertiles of DHEA compared with the lowest tertile are 0.76 and 0.40, respectively (Fig. 1). A monotonically decreasing risk with increasing DHEA levels is suggested, although the test for trend is not statistically significant (P = 0.4). No consistent association between DHEAS and the risk of premenopausal breast cancer is evident.

Smoking has been reported to be associated with DHEA and DHEAS levels, but the association between smoking and premenopausal breast cancer is unclear (15, 16). Because statistical adjustment for the effects of current smoking did not alter the association between DHEA and DHEAS levels and breast cancer, the unadjusted odds ratio are presented.

Parous women are reported to have lower serum levels of DHEA and DHEAS compared with nulliparous women (17, 18). Among parous women, DHEA levels were 17.7% lower among cases compared with controls (14.4 and 17.5 pmol/ml, respectively). DHEAS levels were not different between parous cases and controls (4.4 and 4.3 nmol/ml, respectively). The association for nulliparous women could not be assessed, since only one case and 5 controls were nulliparous at the time of blood collection.

Breast cancer may have been present in some women at the time of blood collection. Thus, the observed association could be related to the presence of cancer on DHEA levels. To assess this situation, we examined the results after stratifying by early diagnosis (those diagnosed within 5 yr of blood collection) and late diagnosis (those diagnosed more than 5 yr from the time of blood collection). Four cases were diagnosed within 5 yr of blood collection. After excluding these cases and their controls, the observed protective effect of DHEA remained unchanged. The associations between DHEA and DHEAS and the risk of premenopausal breast cancer did not significantly vary by time to diagnosis.

DISCUSSION

The finding of an increasing protective association against premenopausal breast cancer with increases in DHEA levels is consistent with other studies of the association between DHEA levels and premenopausal breast cancer (19, 20). In one of these studies, 24-h mean plasma levels of DHEA and DHEAS in samples taken after the diagnosis of premenopausal and postmenopausal breast cancer were compared with levels from normal controls (19). Women with premenopausal breast cancer had subnormal DHEA and DHEAS levels. A prospective study of women on the Isle of Guernsey found lower urinary levels of androsterone, etiocholanolone, and DHEA in women who subsequently developed breast cancer (20). The association was statistically significant only for androsterone. Menopausal status at diagnosis was not specified, but since the age range of the cases was 30 to 55 yr, most cases were presumably premenopausal.
Some studies suggest a difference in the association between DHEA and breast cancer according to menopausal status, but the evidence is inconsistent. In one prospective study of postmenopausal breast cancer, higher levels of DHEA were observed in women who subsequently developed breast cancer compared with matched controls (8). Another prospective study of postmenopausal breast cancer found no difference in age-adjusted DHEAS levels between cases and controls; DHEA levels were not measured (21). A study of 24-h postdiagnostic mean plasma levels of DHEA and DHEAS by Zumoff et al. (19) comparing postmenopausal cases with normal controls showed elevated levels of DHEA and DHEAS levels among cases. However, in another study, women with localized postmenopausal breast cancer diagnosed 1 to 9 yr before the hormonal evaluation had DHEAS levels 7.4% lower than did controls (22). These findings raise the possibility of age-specific responses to DHEA and DHEAS.

DHEA and DHEAS levels have been reported to be lower among parous compared with nulliparous premenopausal women (17, 18). The decrease in DHEA(S) levels occurs after one pregnancy, and the magnitude of the decrease is independent of age at first birth, number of children, or years since last birth (17, 18). This lowering of DHEA(S) has been suggested as a possible mechanism of the protective association between first pregnancy and breast cancer. The results of this study suggest a protective association between DHEA and premenopausal breast cancer among parous women and do not support the hypothesis that the protective effect of age at first birth is through the lowering of DHEA(S). The protective association between pregnancy and breast cancer may be due to other hormonal changes such as effect on estrogen metabolism or prolactin levels (17, 23, 24).

A preventive action of DHEA is biologically plausible. The anticarcinogenic actions of DHEA may operate through its ability to inhibit glucose-6-phosphate dehydrogenase, the enzyme enzyme to the pentose phosphate pathway (2). This pathway generates the reduced form of nicotinamide adenine dinucleotide phosphate and phosphorylated 5-carbon sugars. The former substance is required for biosynthetic processes and is also a cofactor for the metabolic activation of procarcinogens by the cytochrome P-450 system. Phosphorylated 5-carbon sugars serve as precursors for the synthesis of ribo- and deoxyribonucleotides which are ultimately used in the synthesis of DNA and RNA. The antiproliferative and antineoplastic actions of DHEA can be inhibited both in vivo and in vitro by manipulations which supplement animals or their cells with proximal or distal products of the pentose phosphate pathway (2). DHEA also alters the metabolism of procarcinogens and lowers their binding to DNA (3, 5).

A protective association of serum levels of DHEA, but not of DHEAS, with premenopausal breast cancer is suggested by this study. How the antiproliferative action of DHEA might relate specifically to premenopausal but not postmenopausal breast cancer is unknown and clearly suggests the need for further investigation. The sample size, even in this relatively large cohort of women, is limited by the low incidence of breast cancer in young women. Therefore, the results of this study need to be replicated by others before they can be considered generally applicable.

REFERENCES

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