Serum Levels of Dehydroepiandrosterone and Dehydroepiandrosterone Sulfate and the Risk of Developing Gastric Cancer

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Abstract

Although the incidence of gastric cancer varies widely between countries it is nonetheless a leading cause of cancer deaths worldwide. Migration studies indicate that dietary choices are an important exogenous factor. The United States has a very low incidence of gastric cancer, suggesting that exogenous etiological agents are at a minimum and providing a favorable setting for detecting important endogenous etiological factors. Dehydroepiandrosterone and dehydroepiandrosterone sulfate are endogenous steroids produced in the adrenal gland. Epidemiological studies show that the risk of developing specific cancers is related to the serum or urinary levels of these steroids. In addition, dehydroepiandrosterone prevents a variety of spontaneous and chemically induced tumors when administered to laboratory animals. To examine the association between circulating levels of dehydroepiandrosterone and dehydroepiandrosterone sulfate and the development of gastric cancer, we measured the serum levels of these steroids in 13 individuals who donated serum to the Washington County Maryland serum bank in 1974 and who subsequently developed gastric cancer and in 52 matched controls. Prediagnostic serum levels of dehydroepiandrosterone were 38% lower in cases as compared to controls (P = 0.09). The risk of developing gastric cancer increased with decreasing levels of both steroids. Adjustment for confounding factors such as smoking or the interval between blood donation and time to diagnosis did not alter the findings. These results suggest that there may be a role for this steroid in the prevention of gastric cancer.

Introduction

Gastric cancer remains one of the leading causes of cancer death in the world. It is particularly prevalent in areas such as Japan and Chile (1). In the United States the incidence of gastric cancer, the leading cause of death from cancer in 1930, has decreased over 10-fold (2). In 1992 it is estimated that gastric cancer will be diagnosed in 23,800 individuals and account for 13,400 deaths (2). Men will outnumber women by almost 2:1 (2, 3).

Several case-control studies have examined the levels of endogenous hormones including DHEA in patients with gastric cancer. Dehydroepiandrosterone and its sulfate conjugate DHEAS are produced in the adrenal gland in response to adrenocorticotropic (4). Serum levels of these hormones peak in young adulthood and then decrease profoundly and continuously with age as the incidence of proliferative diseases such as cancer and atherosclerosis rises (4–6). The risk of developing specific cancers and atherosclerosis has, in general, been associated with low serum levels of steroids (7–14). Three case-control studies of gastric cancer have consistently found that patients presenting with all but the most advanced stages have a decreased urinary excretion of DHEA(S) relative to controls (15–17). No prospective studies of the association between serum or urine levels of DHEA or DHEAS and the risk of developing gastric cancer have been conducted.

We conducted a nested case-control study to evaluate the association between prediagnostic serum levels of DHEA and DHEAS and subsequent risk for developing gastric cancer. The study is prospective in that the serum was obtained prior to the diagnosis of cancer.

Materials and Methods

Description of the Washington County Serum Bank. The Washington County Serum Bank has been described in detail (18). Briefly, from August through November of 1974, blood samples and basic demographic information were collected from 20,305 residents of Washington County, Maryland. Serum donors were more likely to be better educated, nonsmokers, and women. Participants ranged from 11 to 98 years, with the highest participation rate among those aged 55 to 64 years.

Selection of Cases and Controls. Incident gastric cancer cases were identified by comparing the Washington

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The abbreviations used are: DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate.
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County Cancer Register with the list of donors to the serum bank. Of the 14 cases of gastric cancer (International Classification of Diseases category 159) that developed in this cohort from 1975 to 1989, 13 adenocarcinomas were included, and one, a leiomyosarcoma, was not. Controls were selected from individuals who were alive and free from other cancers, except for nonmelanomatous skin cancers, at the time the case was diagnosed. Four controls were matched to each case by age, sex, race (all cases were white), and hours since last meal.

Measurement of Serum DHEA and DHEAS. DHEA and DHEAS were assayed with commercial radioimmunoassay kits (Wien Laboratories, Succasunna, NJ) according to the directions of the manufacturer, except that hexane:methylene chloride (1:1) was used for the extraction of DHEA. These kits were selected based on comparisons to reference methods for the measurement of DHEA and DHEAS (19).

Statistical Analysis. Because of their skewed distributions, DHEA and DHEAS levels were analyzed as ordered categories or with nonparametric methods. The case and control hormone distributions were compared using the Wilcoxon sign rank test. To account for the matched study design, the Wilcoxon sign rank test comparing the case to the average of its four matched controls was used (20). Tertile cut-off points for DHEA and DHEAS were based on the distributions of the controls. Using the lowest tertile as the referent category, conditional logistic regression was used to obtain maximum likelihood estimates of the matched odds ratios and approximate 95% confidence intervals (21). The strength of the trend in odds ratios with increasing hormone levels was assessed using the likelihood ratio test from the conditional logistic regression equation, with hormone tertile entered as a single quantitative variable (22). The median hormone value for each tertile was used to assign exposure scores for this quantitative variable.

Results
On average, the cases were 61 years old when they donated serum and over 67 years old when they were diagnosed, with a median time to diagnosis of 6.5 years. Comparisons of cases and controls on the matching criteria and other characteristics show no statistically significant differences. More cases than controls had a history of ever smoking (matched odds ratio = 2.6; 95% confidence interval = 0.5 to 14.3). The ratio of males to females was 3:1.

Median DHEA levels were 38% lower in the cases than controls ($P = 0.09$) (Table 1). DHEAS levels were 17.5% ($P = 0.77$) lower among cases than controls. Smoking has been associated with increased levels of DHEA and DHEAS (23) as well as gastric cancer (24) and therefore may confound the association between DHEA and gastric cancer. Adjusting for the effect of cigarette smoking history (ever and never smokers) did not alter the observed associations. The risk of gastric cancer decreased with increasing levels of both DHEA and DHEAS, with the trend slightly stronger for DHEA. Relative to the lowest tertile, high DHEA and DHEAS levels were associated with a 5-fold and 3-fold decrease, respectively, in the risk of developing gastric cancer ($P = 0.06, 0.17$).

Since these findings may be influenced by subclinical disease, reestimates were obtained from analyses limited to the 10 cases diagnosed 3 or more years after donating serum. The trend of decreasing risk of gastric cancer with increasing levels of DHEA and DHEAS remained.

Discussion
The results of this nested case-control study indicate that high serum levels of DHEA up to 14 years prior to diagnosis are associated with a decreased risk of developing gastric cancer. To our knowledge, there are no other studies that have examined the relationship of prediagnostic serum values of DHEA or DHEAS to the risk of developing gastric cancer. The results are consistent with case-control studies which demonstrated that except for individuals with very advanced gastric cancer, patients with gastric cancer have lower urinary excretion of these steroids than controls (15–17).

Although there are no reports of the protective actions of DHEA in animal models of gastric cancer, DHEA has an impressive spectrum of activity in tissue culture systems and in animal models of both cancer and atherosclerosis (25–29).

In any cohort study the possible effects of a bias introduced by different losses to follow-up among cases and controls should be considered. However, the Washington County population has a low rate of outmigration (1%/year), and case ascertainment is estimated to be reasonably complete. Therefore this is unlikely to affect the observed results of this study. While the observed association may not be a direct protective effect by DHEA or DHEAS but rather an effect of some other factor(s) for which it is a surrogate marker, animal experimental studies suggest a direct protective effect by DHEA against cancer. Despite the small size of this study, we have found a strong, inverse, dose-related association between serum levels of DHEA and the risk of developing stomach cancer.

Table 1 Median DHEA and DHEAS levels (and interquartile-range) among gastric cancer cases and controls.

<table>
<thead>
<tr>
<th>Steroid hormone (units)</th>
<th>Cases (n = 13)</th>
<th>Controls (n = 52)</th>
<th>Percentage difference</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA (pmol/ml) (1.56 to 6.89)</td>
<td>7.02</td>
<td>-37.9</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>DHEAS (mmol/ml) (1.29 to 1.42)</td>
<td>2.75</td>
<td>-17.5</td>
<td>0.77</td>
<td></td>
</tr>
</tbody>
</table>

* Calculated as [(case median - control median)/control median] × 100.

References


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