A Prospective, Population-based Study of Androstenedione, Estrogens, and Prostatic Cancer

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ABSTRACT

Endogenous androgens have been suggested as determinants of risk of prostatic cancer. To examine this possibility, baseline sex hormone levels were measured in 1008 men ages 40-79 years who had been followed for 14 years. There were 31 incident cases of prostatic cancer and 26 identified from death certificates with unknown dates of diagnosis. In this study, total testosterone, estrone, estradiol, and sex hormone-binding globulin were not related to prostate cancer, but plasma androstenedione showed a positive dose-response gradient. Age-adjusted relative risks of prostatic cancer for low (0.0-2.2 nM), middle (2.3-3.1 nM), and high (3.2-4.0 nM) tertiles of androstenedione were 1.00, 1.34, and 1.98, respectively (P trend < 0.05). The linear gradient of risk persisted after adjustment for age and body mass index. If confirmed, these data suggest that androstenedione might increase the occurrence of clinically manifest prostatic cancer.

INTRODUCTION

In men in the United States, prostatic cancer has the third highest age-adjusted incidence rate of any cancer and is the third leading cause of cancer death (1). The epidemiology of prostatic cancer (2-8), sex hormone levels in men (9-13), and hormonal influences on the prostate (14) have been reviewed previously. Endogenous sex hormones, have been proposed as risk factors for prostatic cancer, but results from existing cross-sectional or case-control studies are conflicting. Thirteen studies have reported plasma testosterone levels in prostatic cancer cases compared to controls; one compared testosterone levels in cases to normal values from the same laboratory; and one compared testosterone levels in cases to testosterone levels in men with benign prostatic hypertrophy. Six studies observed lower levels in cases than in controls (15-19) or laboratory normals (20), and three reported higher levels (21-23). Other studies observed higher levels in some subgroups and lower in others (24-28).

Ten case-control studies reported estradiol levels: four reported lower levels in cases (15, 16, 19, 22); four reported higher levels in cases than in controls (18, 20, 23, 27); and one reported equal levels in cases and controls (17). Nigerian cases had lower levels of estradiol than Nigerian controls, but Washington, DC, black cases had higher levels than their controls (26).

Of the seven case-control studies that reported estrone levels, three reported higher levels in cases (18, 24, 27), two reported lower levels in cases (14, 18), and one reported equal levels in cases and controls (16). Nigerian cases had a level of oestrone identical to that in Nigerian controls, but Washington, DC, black cases had slightly higher levels than Washington, DC, controls (26).

Only three case-control studies reported androstenedione levels; one reported lower (18), one slightly lower (17), and one higher (15) levels in cases. All three studies reporting levels of sex hormone-binding globulin reported higher levels in cases than in controls (16, 19, 20).

No previous prospective, population-based study of endogenous sex hormone and sex hormone-binding globulin levels and subsequent fatal and nonfatal prostatic cancer has been reported. We report such a study in 1008 men ages 40-79 years who were followed for 14 years.

MATERIALS AND METHODS

During 1972-1974, 82% of the residents of Rancho Bernardo, CA, a white upper middle class community near San Diego, were surveyed for heart disease risk factors as part of a Lipid Research Clinic Prevalence Study (29). All participants had a standardized interview, including questions about life-style. Cigarette smoking was characterized at the time of interview as never, past, or current. Weight and height were measured with participants in light clothing without shoes: obesity was estimated by body mass index (weight (kg)/[height (m)]2). All blood samples were obtained between 7 and 11 a.m.; 95% of participants had fasted, as requested, 12-16 h prior to venipuncture. The cohort was followed at intervals for morbidity and annually for vital status for 14 years, with 99.9% ascertainment. Death certificates were obtained for all decedents and coded for cause of death by a certified nosologist according to the International Classification of Diseases, Ninth Revision (30). Prostatic cancer (ICD 185) was listed as the underlying cause of death on 18 certificates and a contributory cause on 8 certificates.

Prostatic cancer was ascertained by mailed questionnaire in 1983 and 1985 and by interview in 1984-1987. All 18 incident cases reported during 1 year, 1983, were found to be valid after examination of physician or hospital records. Since the validation rate observed for incident cases in 1983 was 100%, no attempt was made to validate later incident cases. For cases ascertained from death certificates, validation was attempted in five, and the diagnosis was confirmed in all four cases where the next of kin gave permission to release hospital records. The date of diagnosis of cases ascertained only from death certificates was uncertain; date of death was used as date of onset in the analyses.

Plasma obtained at baseline (1972-1974) and maintained at −70°C was thawed in 1985-1986 for sex hormone and sex hormone-binding globulin determination. Previous work in this laboratory has shown that steroid hormone levels remain constant in sera frozen for up to 15 years. The 1008 plasma samples assayed were chosen without knowledge of baseline or subsequent disease status, the number being determined only by availability and cost constraints. Concentrations of androstenedione, testosterone, estradiol, and estrone were determined by radioimmunoassay (31-33). In this laboratory, the sensitivity, intraassay coefficient of variation, and interassay coefficient of variation for these hormones are, respectively: androstenedione, 0.105 nm, 4.0 and 8.0%; testosterone, 0.087 nm, 4.1 and 10.0%; estradiol, 0.018 nm, 8.0 and 12.0%; oestrone, 0.026 nm, 15.0 and 16.0%. Sex hormone-binding globulin was determined by the method of Rosner (34).
Table 1 Median, 25th, and 75th percentiles of plasma sex hormones in nmol/liter: prostatic cancer cases and noncases ages 40–79 years at baseline, Rancho Bernardo, CA, 1972–1986

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Cases 25th</th>
<th>Cases 50th</th>
<th>Cases 75th</th>
<th>Noncases 25th</th>
<th>Noncases 50th</th>
<th>Noncases 75th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androstenedione (N = 1004)</td>
<td>2.05</td>
<td>2.84</td>
<td>3.75</td>
<td>2.13</td>
<td>2.70</td>
<td>3.40</td>
</tr>
<tr>
<td>Testosterone (N = 1001)</td>
<td>14.6</td>
<td>18.4</td>
<td>23.4</td>
<td>14.6</td>
<td>18.0</td>
<td>22.1</td>
</tr>
<tr>
<td>Estradiol (N = 1004)</td>
<td>0.12</td>
<td>0.14</td>
<td>0.16</td>
<td>0.11</td>
<td>0.13</td>
<td>0.16</td>
</tr>
<tr>
<td>Estrone (N = 1004)</td>
<td>0.15</td>
<td>0.18</td>
<td>0.22</td>
<td>0.13</td>
<td>0.17</td>
<td>0.22</td>
</tr>
<tr>
<td>Sex hormone-binding globulin (N = 976)</td>
<td>18.8</td>
<td>29.0</td>
<td>42.5</td>
<td>21.2</td>
<td>28.6</td>
<td>40.5</td>
</tr>
</tbody>
</table>

* No differences were statistically significant according to the Wilcoxon rank test.

Since hormone levels were not normally distributed in the cases, the Wilcoxon rank test (35) was used to compare hormone levels between cases and all other men. The distribution of sex hormones was divided into tertiles and age-adjusted rates of prostatic cancer were computed for each tertile. Age adjustment was done by Mantel-Haenszel analysis (36) using the age distribution of the entire study population of men ages 40–79 years as the standard. Relative risks were calculated after adjustment for age and body mass index (kg/m²), using Cox proportional hazards regression (37). The Mantel extension test was used to test for trend (38). The statistical analyses were performed using the Statistical Package for the Social Sciences (39) and BMDP (40). All P values are 2-tailed and no adjustment was made for multiple testing.

RESULTS

Among these 1008 men there were 57 cases of prostatic cancer during the 14 years following the baseline examination (when blood was drawn for sex hormone assays). The interval between the baseline examination and the reported date of diagnosis of prostatic cancer (N = 31) or prostatic cancer-related death (N = 26) averaged 8.1 years with a range of 1–14 years. The 57 prostatic cancer cases were significantly older (67.4 ± 7.4 years) than the 951 noncases (63.2 ± 9.6 years; P ≤ 0.001). Age-adjusted rates of current cigarette smoking were not significantly different in cases (25%) versus noncases (19%), nor was age-adjusted body mass index, in cases (26.15 ± 2.73 kg × kg/m²) versus noncases (25.78 ± 3.01 kg/m²).

Unadjusted median hormone levels in men with and without prostatic cancer were similar (Table 1). When analyzed by tertile, there was no association between plasma testosterone, estradiol, estrone, or sex-hormone binding globulin levels and risk of prostatic cancer (Fig. 1, B–E). The positive trend for plasma estradiol and prostatic cancer (Fig. 1C) was not statistically significant (P trend = 0.11). There was a statistically significant association between plasma androstenedione and prostatic cancer (P trend < 0.05; Fig. 1A). The association with androstenedione persisted after adjustment for age and body mass index according to Cox proportional hazards regression (Table 2). The age-adjusted relative risks of prostatic cancer for low (0–2.293 nm), middle (2.294–3.153 nm), and high (3.154+ nm) tertiles of androstenedione were 1.00, 1.34, and 1.98, respectively (P trend < 0.05). These estimates are based on 16 cases among 335 men at risk in the lowest tertile, 20 cases among 345 men at risk in the middle tertile, and 21 cases among 345 men at risk in the middle tertile, and 21 cases...
among 324 men at risk in the highest tertile (Fig. 1A). The relative risk of prostatic cancer for an increase in plasma androstenedione of 1.17 nM (1 SD) was 1.26 (95% confidence limits 1.04–1.54) after adjusting for age, or age and body mass index (Table 3). Similar results were observed when cigarette smoking was included as a covariate (not shown). No association between any of the other hormones or sex hormone-binding globulin and prostatic cancer was observed.

An analysis of the nonfatal cases showed only a corresponding but nonsignificant positive trend for androstenedione (0.25 > P trend > 0.10). Another analysis that excluded the men who died within 5 years (N = 5) or had a date of diagnosis within 5 years (N = 8) of baseline showed similar trends (data not shown).

**DISCUSSION**

It has been known for over 200 years that castration leads to prostatic atrophy (41) and it has been reported that prostatic cancer is rare or nonexistent in men with a lifetime absence of testicular androgen (42). Several lines of evidence suggest that testicular androgen is essential to the development of prostatic cancer: prolonged administration of testosterone (43, 44) and of estrogen followed by testosterone (43, 45) induces prostatic cancer in some experimental animal models; administration of testosterone with carcinogens (46–48) or promoters (49) induces prostatic cancer in other animal models; receptors for sex hormones have been found in hyperplastic human prostatic tissue (50–53), normal rat prostatic tissue (54, 55), human prostatic cancer (56–59), and a human prostatic cancer cell line (60); prostatic cancer is clinically responsive to orchiectomy (61) and adrenalectomy (62, 63) and to endocrine manipulation using a hormone that competes with androgens for receptor sites in the prostate (64–67), or with aminoglutethimide or other agents which block adrenal production of androstenedione (68–70).

Plasma androstenedione as a risk factor for prostatic cancer has been studied previously in only three studies, all cross-sectional. In Wales (15) there were nonsignificantly higher levels of plasma androstenedione in cases than in controls; in South African blacks (18) cases had significantly lower levels than controls and in Finland (17) cases and controls had similar levels. In the present study we found a significantly higher level of androstenedione in cases after adjustment for age, body mass index, and smoking, the principal attributes known to be associated with sex hormone levels (10, 12, 13).

Dihydrotestosterone, an active metabolite of testosterone in the prostate, has been detected previously in the prostates of some prostatic cancer patients who had been orchiectomized (or were receiving estrogen therapy) at levels higher than those present in intact normal males (71). Adrenal androgens provide approximately one-fifth of the dihydrotestosterone present in the prostate (67). Androstenedione converts to dihydrotestosterone (72), estrone (73), and estradiol (74) in the prostate. The rate of aromatization of androstenedione to estrogens is highest in the peripheral zone (74), which is the usual site of prostatic cancer (75).

Plasma sex hormone levels correlate poorly with prostatic cancer (76) and in the present study the relative risk of prostatic cancer for an increase in plasma androstenedione (1.17 nM) was 1.26 (95% confidence limits 1.04–1.54) after adjusting for age, or age and body mass index (Table 3). Similar results were observed when cigarette smoking was included as a covariate (not shown). No association between any of the other hormones or sex hormone-binding globulin and prostatic cancer was observed.

An analysis of the nonfatal cases showed only a corresponding but nonsignificant positive trend for androstenedione (0.25 > P trend > 0.10). Another analysis that excluded the men who died within 5 years (N = 5) or had a date of diagnosis within 5 years (N = 8) of baseline showed similar trends (data not shown).
tissue levels, and the latter may be more important in determining prostatic cancer risk (76, 77). Some of the inconsistencies among previous studies may reflect the problems of case-control design; e.g., the disease may change plasma hormone levels or the control groups may be inappropriate. The results of prospective studies of hormones may differ importantly from those of case-control studies (78).

To our knowledge this is the first prospective study of sex hormones and prostatic cancer. Results will need to be confirmed. Nevertheless, the association with androstenedione reported here is provocative and compatible with an effect of adrenal androgen, either directly or via its metabolites, on prostatic cancer.

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ANDROSTENEDION K AND PROSTATIC CANCER

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